1 DEPARTMENT OF HE

FOOD AND DRUG ADMINISTRATION CENTER

FOR DRUG EVALUATION AND RESEARCH
THE PEDIATRIC SUBCOMMITTEE
OF THE ANTI-INFECTIVE DRUGS
ADVISORY COMMITTEE

IN JOINT SESSION WITH

THE PEDIATRIC
SUBCOMMITTEE
OF THE ONCOLOGIC DRUGS ADVISORY
COMMITTEE

(ODAC)

Tuesday, September 12,

2000

8:00 a.m.
Hyatt Regency Bethesda One
Bethesda Metro Center
Bethesda, Maryland

2 PARTICIPANTS

P. Joan Chesney, M.D., Chairperson
Karen M. Templeton-Somers, Executive
Secretary

THE ANTI-INFECTIVE DRUGS SUBCOMMITTEE

MEMBERS:
Judith O'Fallon, Ph.D.
Keith Rodvold, Pharm.D. (Consumer
Representative)

SGE CONSULTANTS:
David Danford, M.D.
Robert Fink, M.D.
Susan
Fuchs, M.D.
Barbara Geller,
M.D.
Richard Gorman, M.D.,
FAAP Mark Hudak, M.D.

Naomi Luban, M.D.
Robert Nelson, M.D., Ph.D.
Victor Santana, M.D.

GUESTS AND GUEST SPEAKERS:
Ralph Kauffman M.D.
Steven Spielberg, M.D., Ph.D. Robert Ward, M.D., FAAP, FCP

THE ONCOLOGIC DRUGS SUBCOMMITTEE MEMBERS:
Victor M. Santana, M.D.
Donna Przepiorka, M.D., Ph.D.

AD HOC MEMBERS:
James M. Boyett, Ph.D.
Susan L. Cohn, M.D.
Alice Ettinger, MSN, RN, CPON, CPNP Jerry Z. Finklestein, M.D.
Henry S. Friedman, M.D.
C. Patrick Reynolds, M.D., Ph.D.

PATIENT ADVOCATE:
Susan L. Weiner, Ph.D.

GUESTS AND GUEST SPEAKERS:
Frank M. Balis, M.D.
Malcolm Smith, M.D., Ph.D.

FDA:
Steven Hirschfield, M.D., Ph.D. Richard Pazdur, M.D.
Dianne Murphy, M.D.

3 C O N T E

P R O C E E D I N G S

Call to Order

DR. CHESNEY: Good morning. I think we are ready to start, and before we get into discussion I would like to just say thank you to Dr. Murphy and all of her staff at the FDA who have done such an incredible job of organizing these two days with four totally unrelated subjects, except that

they all relate to pediatrics, and also to let you all know that in the "Science Section" of The New York Times today, in the middle, there is a full-page article, with a big picture of Dr. Murphy, and all addressing the use of drugs in children. So, I think that is a real tribute to her and to all of the efforts of the FDA in this regard.

We are going to start by having everybody introduce themselves, and also to remind you all that when you ask a question or make a comment, please be sure to give your name so the transcriber will know who it is and, for those of you who weren't here yesterday, the way to turn on your microphone is to push the green button. So, let's start over here, on the left-hand side. I think Dr. Murphy is the first.

DR. MURPHY: Dianne Murphy, Associate Director for Pediatrics at CDER, and I haven't read the article so I don't know if I am infamous or not.

[Laughter]

DR. PAZDUR: Richard Pazdur, Division Director, CDER.

DR. HIRSCHFIELD: Steven Hirschfield, medical officer, Division of Oncology Products. I read the article and it is very favorable.

DR. SMITH: Malcolm Smith, head of the Pediatrics Section of the Cancer Therapy Evaluation Program and pediatric oncologist.

DR. BALIS: Frank Balis. I am a senior investigator at the National Cancer Institute, Pediatric Oncology Branch.

DR. BOYETT: James Boyett, chairman of the Department of Biostatistics at St. Jude Children's Research

Hospital.

DR. COHN: Susan Cohn, and I am on staff as a pediatric oncologist at Children's Memorial in Chicago.

DR. PRZEPIORKA: Donna Przepiorka, marrow transplanter, Baylor College of Medicine, Houston.

DR. WEINER: I am Susan Weiner. I am president and founder of The Children's Cause. I was a parent.

DR. REYNOLDS: I am Patrick Reynolds, Children's Hospital of Los Angeles.

DR. FRIEDMAN: Henry Friedman, Brain Tumor Center at Duke.

MS. ETTINGER: Alice Ettinger. I am a pediatric

nurse practitioner in New Brunswick, New Jersey.

DR. FINKLESTEIN: I am Jerry Finklestein. I am a pediatric oncologist in Long Beach, and also chair

hematology oncology for the American Academy of Pediatrics.

DR. CHESNEY: Joan Chesney. I am in infectious diseases at the University of Tennessee, in Memphis, and also in academic programs at St. Jude.

DR. TEMPLETON-SOMERS: Karen Somers. I am the executive secretary to the Oncologic Drugs Advisory Committee, FDA.

DR. SANTANA: Victor Santana, pediatric oncologist at St. Jude Children's Research Hospital in Memphis, Tennessee.

DR. NELSON: Skip Nelson. I am a pediatric clinical care physician at the Children's Hospital in Philadelphia.

DR. GORMAN: Richard Gorman, general pediatrician in private practice in suburban Maryland.

DR. O'FALLON: Judith O'Fallon, group statistician

for the North Central Cancer Treatment Group.

DR. RODVOLD: Keith Rodvold, professor of pharmacy practice, colleges of pharmacy and medicine, University of Illinois, Chicago.

DR. GELLER: Barbara Geller, professor of psychiatry, Washington University in St. Louis.

DR. DANFORD: Dave Danford. I am a pediatric oncologist at the University of Nebraska Medical Center and Creighton University in Omaha.

DR. FUCHS: Susan Fuchs, pediatric emergency medicine physician in Children's Memoria Hospital, Chicago.

DR. HUDAK: I am Mark Hudak. I am chief of Neonatology at the University of Florida at Jacksonville.

DR. FINK: Bob Fink, pediatric pulmanologist, Children's Hospital, Washington, DC.

DR. LUBAN: Naomi Luban, pediatric

hematologist-
oncologist, for this group mostly a hematologist, Children's Hospital, Washington, DC.

DR. SPIELBERG: Steven Spielberg, head of pediatric drug development at Johnson & Johnson, representing PhARMA.

DR. KAUFFMAN: Ralph Kauffman, pediatrician, clinical pharmacologist, Children's Mercy Hospital, Kansas City, Missouri.

DR. WARD: Bob Ward, neonatologist and professor of pediatrics, University of Utah, and chair of the American Academy of Pediatrics Committee on Drugs.

DR. CHESNEY: Thank you. Karen Templeton-Somers, our executive secretary, is going to read the conflict of interest statement.

Conflict of Interest Statement

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with

regard to

this meeting, and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interest reported by the committee participants, it has been determined that since the issues to be discussed by the subcommittee will not have a unique impact on any particular firm or product but, rather, may have widespread implications to all similar products, in accordance with 18 USC 208(b), general matters waivers have been granted to each special government employee participating in today's meeting. A copy of this waiver statement may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of

the Parklawn Building.

With respect to FDA's invited guests and guest speakers, Dr. Ralph Kauffman, Dr. Steven Spielberg and Dr. Robert Ward have reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Kauffman would like to disclose that he has grants with Bristol-Myers Squibb and is involved in research for Bristol-Myers Squibb, Astra, Zeneca, Janssen, Merck, R.W. Johnson and Adventis, and is a scientific advisor for

Bristol-Myers Squibb, Johnson & Johnson and Purdue PhARMA.

Dr. Spielberg would like to disclose that he is an employee of Johnson & Johnson. Dr. Ward would like to disclose that he owns stock in Ascent Pediatrics and

Viropharma; has grants with Wyeth-Ayerst, Novardis, Ascent Pediatrics, Adventis Pharmaceutical and Sepracor; receives consulting fees from Janssen Pharmaceutical and is a scientific advisor for McNeil Consumer Products.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon. Thank you.

DR. CHESNEY: Does anybody have anything that they

haven't yet declared? Hearing none, Dr. Murphy will give us our mission for the morning.

Introduction to the Issues

DR. MURPHY: Actually, I am going to try to do a little more than that -- I try not to tell the chair what we are going to do.

[Laughter]

It is basically part of our responsibility, under the Pediatric Rule, to provide an update to this pediatric subcommittee on an annual basis.

[Slide]

As yesterday was even busier with a packed schedule, I chose this morning and I would like to take about five minutes of today's time to update the pediatric subcommittee on where we are.

[Slide]

I am leaving this up because I don't want to have

slide after slide of the statistics of what has been going on because you heard some of that yesterday as far as over 150-some written requests that we have issued under the Food and Drug Modernization Act and the fact that we expect 85 percent, approximately 75-85 percent of those studies to be completed.

The other activities that have been ongoing in the meantime are rather significant and I would like to take a moment and introduce Dr. William Rodriguez. Dr. Rodriguez, would you stand up, please? He introduced himself yesterday. He has come to us as our science advisor because it has become quite clear to us, as we move into the whole area of drug development, that we have a tremendous number of questions as we go forward in how we do drug development

in children and the science gaps are significant in certain areas. Dr. Rodriguez was a professor of pediatrics at Children's Hospital in Washington for 29 years and is now professor emeritus, and we are delighted to have him join us, and you will be seeing more of him as he begins to address some of the issues that we know exist. As a matter of fact, I think Thursday is his first internal brainstorming session for us in the agency, and we will have a number of those.

The other aspects that I wanted to inform the committee about were the fact that we have a congressional report that is due January 1 on the effectiveness and efficacy, if you will, of the legislation, and we will have that report out of the Center by the end of this month and

anticipate that we will be bringing that report to you next year, after it is made public, that answers the questions that we were mandated by Congress to answer about the implementation of the Modernization Act.

I said to Rosemary this is beginning to get embarrassing, and she said, what do you mean, beginning to get? -- Dr. Roberts told me it is embarrassing. We had stated last year that we thought we would have the guidance on the Pediatric Rule out by June. It is not. We are pushing very strenuously to have it out before December.

The Pediatric Rule went into effect for the agency as far as

our responsibility to inform sponsors that they must have either studies in their applications or they must have a waiver or deferral from us -- that began in

April of 1999.

We could not require studies until this December. So we were informing them but we could not require they submit them. We can require them to have those studies as of this December. We hope to have the guidance out before that point.

One last thing for the committee to be aware -- you heard yesterday that there are continuing ethical issues that we may need to bring to you but, in particular, we will be bringing some of the issues attendant to extrapolation and the algorithms that we are developing are building upon some of the data that is coming in and experiences we have had with concentration response studies and the use of PK/PD in our development program. So, we hope in the upcoming year to be able to bring some of that

information to the
committee. At this point, we have had -- and this is all
available as public documents on the web, the address of
which the committee is very familiar with at this point --
we have had 24 products bring their studies in for an
exclusivity determination, and we have 11 of those products
already labeled. And, people say, "why do you say already?"
I don't need to explain to this group that from the time we
issue a written request to the time that the sponsor has to

develop the protocol, recruit the researchers, put the study
in place, collect the data, submit it, review it and then
send it in to us we have 10-12 months to review it. That is
fairly phenomenal since the first request was in July of
'98. So, in the last two years we have had

24 products
 6 submitted for exclusivity determination and
have already
 7 been able to label 11, and we have another
one and I was
 8 hoping I would be able to tell you an even dozen
but it is
 9 close. So.
10 Now, as far as the Pediatric Rule is
concerned, as
11 I said, it went into effect April, 1999. We are
requiring
12 the studies as of December. What has happened
with waivers
13 and deferrals thus far?
14 [Slide]
15 This is an overview, and I really
would tell the
16 committee at this point that my intent this
morning is not
17 to provide you any details on these but to give
you the
18 broad-brush overview as to what is happening
because, again,
19 we can't require the studies to come in. So, in
the
20 categories of diseases where are we waiving and

where are we
21 deferring products this coming year we will provide more
22 detail as to what is happening within some of these
23 categories.
24 You can see that in cardiorenal, which leads the
25 pack as far as written requests and/or exclusivity, we have

1 had two waivers -- usually this is because of a disease that
2 would not exist in children -- and one deferral. The areas
3 of activity under exclusivity are cardiorenal, neuropharm.,
4 metabolic, anesthetic and antivirals. So, right now it
5 would appear that most of the studies that are being
6 deferred are in metabolic, and as we discussed yesterday,
7 what that means is really a spectrum of activities. It may
8 mean that we know really what the protocol is. It may even

be as developed as a Phase IV requirement. Or, it may be, as we discussed yesterday, that we think pediatric studies will be required but we are at that point that I mentioned earlier where we don't feel competent enough; there is not a level of certainty that we want to proceed in asking or demanding that these studies be done until we have additional data. So, we have a large category of deferrals at this point as we build up some of the information bases that allow us to design those studies that we are going to be requiring.

[Slide]

As I said, in antivirals are studies that have come in. So, you aren't seeing the studies that have come in. Even though they are not required, they have come in under the FDAMA. Because this process has

turned out to be
24 much more complex than I am sure any of us anticipated, in
25 any one application that is in-house we may have a waiver, a

1 deferral and studies. All three things can be happening
2 with the same product. Depending on whether that disease
3 occurs in the entire spectrum of pediatrics, you may have
4 some part that you are waiving; you may have another part
5 which you are deferring because you are waiting on the
6 information that you have on the studies that you have in-
7 house. So, all three things may be happening in some areas.
8 [Slide]
9 This is to give you a feel for the activity. We
10 are trying to present this in a less crowded way. We
11 normally send you these statistics as they are up on the web

and they are not particularly viewer friendly, but these slides now break out for you the various disease categories which are really our divisions, and the numbers of proposals that sponsors have sent in to us, in the left-hand column, and the number of written requests that we have issued for studies to be done in these areas. Again, this is under exclusivity. I just finished going over the rule. Exclusivity has been effective since 1997. In July of '98 we had our first written request issued.

So, quite a few studies have been asked for in cardiorenal and neuropharm. I iterate one more time that these are voluntary. The sponsors do not have to do them, but we have some changes from last time in some of these categories in that we have had increased activity in

metabolic, endocrine and anti-inflammatory, and

gastroenterology, special pathogens and oncology.

[Slide]

This slide is to lead me into the topic for this morning. In the implementation of FDAMA, it is quite clear that not only do all diseases have their own special needs and areas of development as far as the science base and as far as the clinical trials base, in the area of oncology it is -- how should I -- I am told you can't be "very" unique; you are just unique -- they are unique, and we have -- I will use the word struggled because we have to treat all diseases the same in that many a parent who has a child with a severe neurologic disease, a parent who has a child who is dying from heart disease -- these are all as serious and important to them as any disease. So, we need to do things

that are consistent with an even playing field for the development of all of these areas. We found there were unique aspects that we needed to address for oncology, and to do that we really discussed it with a number of external experts.

[Slide]

And, the American Academy of Pediatrics put together an invitational meeting in February of this year and invited a number of academic researchers, National Cancer Institute, PhARMA, pediatric cooperative groups,

advocacy representatives and, of course, the FDA. We discussed the issues surrounding pediatric drug development in the area of oncology, and felt that we were able to define a process and that is one of the things that we hope to accomplish this morning, to present this approach to you.

There is a guidance, in contrast to the Pediatric Rule guidance, just to let you know the level of priority that was put on this. We got this guidance out in record time because we did not want this to continue without information for the researchers and the sponsors in how we were looking at the development of this area because it is different. And, that is what will be explained to you this morning.

In addition to the process, there is a new committee that has been put in place and I will ask Dr. Hirschfield to, please, come up here and explain to you the development of an additional -- let me back off; I am not allowed to say we have a new advisory committee, so an additional panel of experts which we are utilizing to advise us. Thank you.

DR. HIRSCHFIELD: Good morning. I would like to acknowledge the efforts and the support that Dr. Mack Lumpkin, our Associate Center Director, Dr. Dianne Murphy, our Associate Center Director for Pediatrics, and Dr. Richard Pazdur have provided on behalf of and in support of pediatric oncology, and none of what we are going to discuss

over the course of the day would have gone forward without their efforts.

We recognized, and you will hear several times during the course of the morning and those who go to the afternoon session on pediatric oncology, how pediatric oncology has characteristics that are different than other areas in pediatrics. The diseases are relatively rare. They are life-threatening. There is also a long

history of
evidence-based medicine, going back essentially fifty years.
Most of the children are treated on protocols in cooperative
group studies and there is a recognition that research is
the standard of care for pediatric oncology. You will hear
these themes again, but these themes made us examine very
carefully the approaches that were taken to other pediatric
diseases and ask how can we adapt the tools that we have,
which are new in the history of regulatory science, to the
pediatric oncology situation?
And, one of the mechanisms was to look at how we
could apply the Pediatric Rule. The Pediatric Rule states
that if a disease in adults is similar to a disease in
children, or vice versa, there is a mandate to perform
studies in the pediatric population.

There is also an
23 incentive in the sense that it is possible, if efficacy is
24 demonstrated, to apply the adult efficacy data to the
25 pediatric population.

1 Pediatric oncology has yet another difference,
2 aside from the differences just enumerated and that is that
3 the biology of the tumors tends to be quite different from
4 the tumors which are seen in adults. Adults typically get
5 tumors associated with the skin, the lining of the skin, the
6 lining of the lungs, breast, and pediatric tumors tend to
7 have different tissue origins. So, on the surface it looked
8 like the Pediatric Rule would be extremely limited in its
9 application, perhaps to some brain tumors; perhaps to some
10 hematologic tumors. But otherwise we would have the

inability to utilize what we perceive as a very important tool.

However, we decided to examine that question. So, we convened a panel of experts and supplemented what we consider our core group of experts with experts who will be coming for today to assist us in describing the characteristics of tumors, and we will be spending the afternoon asking the question how do we describe tumors? What is it we know about tumors? What are the principles that we can use to extend our knowledge of one tumor type to another tumor type?

In that regard, aside from the distinguished panel that has introduced themselves to you this morning, we will have Dr. Todd Gollup from the Whitehead Institute join us. Dr. Gollup, for those of you who happen to have read this

week's Science magazine, was featured in the "News and Views" for his work on DNA micro arrays in describing tumors.

Dr. Michelle LeBeau, of the University of Chicago, who is an authority on cytogenetics, will discuss with us this afternoon the application of cytogenetics to tumor characterization. Dr. David Parma, of the University of Arkansas, who is a world recognized expert in the histopathology of tumors; Dr. Peter Berger, of Johns Hopkins University, who is internationally recognized for his work on pediatric and adult brain tumor pathology. In addition, although he is part of our regular panel too, Dr. Frank Balis, of the National Cancer Institute, will offer his perspectives on the application of development of

15 therapeutics.

16 This panel, we hope, will stretch the boundaries

17 of what is now only known about pediatric oncology but help

18 set a precedent for the examination of how one may

19 extrapolate our knowledge of adult diseases to pediatric

20 diseases, not only for the regulatory purpose but for

21 scientific purposes that we can think of different

22 paradigms, perhaps new paradigms in terms of combining

23 studies in certain cases between adults and children,

24 looking at the types of information that we would need to

25 make not only regulatory decisions but therapeutic and

1 scientific decisions.

2 I look forward, and feel honored to be part of

3 this day today. Thank you very much.

4 DR. CHESNEY: Thank you, Dr. Murphy

and Dr.
Hirschfield. Our first speaker this morning is Dr. Malcolm
Smith, from the National Cancer Institute, and he is going
to talk to us about the application of evidence based
medicine to achieve progress in pediatric oncology.

The Application of Evidence-Based Medicine to Achieve
Progress in Pediatric Oncology

DR. SMITH: It is a privilege to speak to you
today on the application of evidence-based medicine to
achieving progress in pediatric oncology.

[Slide]

In many ways, I am speaking to you today on behalf
of the hundreds of clinical researchers who, over the past
four decades, have designed and conducted the clinical
trials that have led to the progress that I will be
describing, and speaking on behalf of the

thousands of
20 patients and their families who have
participated in these
21 trials.
22 [Slide]
23 As an outline of what I will be
speaking about,
24 first I will give an introduction and historical
25 perspective. Then, I will speak about the
importance of

1 Phase III randomized clinical trials to the
progress that we
2 have achieved in treating children with cancer.
I will talk
3 about the importance of risk-adjusted therapy to
developing
4 better treatment strategies for children with
cancer. I
5 will talk about the clinical trials research
infrastructure
6 that has been essential to this progress, and I
will end by
7 talking about unmet needs and future directions.
The
8 handouts that you have, have additional details
beyond the

slides that I will be using today.

[Slide]

First in terms of childhood cancer basic introduction, a few points: There are 8700 new cases of cancer diagnosed annually among children younger than 15; over 12,000 when you extend the age limit up to younger than 20 years of age. There are approximately 1700 children who die each year of cancer younger than 15 years of age, and over 2000 when you extend the age to up to 20 years of age, making cancer the leading cause of disease-related mortality among children over one year of age. Finally, most of the cancers of children differ from those of adults in their histology and in their biological characteristics.

[Slide]

This slide shows the distribution of cancers that

occur in adults, and you will recognize prostate cancer, breast cancer, lung cancer, colorectal cancer. These are

the carcinomas that predominate in adults.

[Slide]

Whereas in children, this slide shows the distribution and approximately half of the cancers among children are divided between the leukemias, acute lymphoblastic leukemia predominating, and the brain tumors. Then, there are tumors like neuroblastoma, Wilm's tumor and retinoblastoma that have no equivalent among adults. Even the tumors that have the same name, like non-Hodgkin's lymphoma or acute lymphoblastic leukemia -- the subtypes that occur in children are often distinctive from the types that occur in adults.

[Slide]

So, in terms of childhood cancer clinical research, one basic principle is that national efforts are essential for studying the specific childhood cancers because of the limited numbers of children with individual cancer types. So, in recognition of this fact, the NCI has supported, since the 1950s, a nationwide clinical trials program specifically designed to improve the outcome for children with cancer.

[Slide]

A second basic principle is that we need to have separate studies and we need to have a separate research structure for studying the cancer in children. Again, the

cancers of children are biologically distinctive in most cases from those that occur in adults, and so the response of children to anti-cancer treatments may be

qualitatively
4 or quantitatively different from response of adult cancers.
5 Second, the ability of children to tolerate anti-
6 cancer treatments may differ from that of adults. Children
7 may be more sensitive or less sensitive to specific drugs
8 and it may depend on age, different doses of drugs, and
9 different schedules of drugs may need to be used.
10 Also, the investigators with special expertise in
11 pediatric oncology are the ones that are really best
12 qualified to prioritize, design and implement the clinical
13 trials for children with cancer.
14 [Slide]
15 We, in part, are still invested in our system of
16 clinical research because of the results that have been
17 achieved with this system. When we looked at the early

1960s, only a small minority of children were cured of their cancers. However, currently the survival rates for children with cancer approach 75 percent. The mortality rate from childhood cancer has decreased nearly 50 percent from 1973 to 1996, and this decline in mortality rate has continued in the 1990s at a rate of approximately 3 percent per year.

[Slide]

I will give two specific examples of these

improvements in outcome. The first is the example of leukemia. Mortality remained relatively constant through the 1950s and the mid-1960s. Since the mid-1960s mortality rate for leukemia has declined.

[Slide]

And, the reason for this decline is not that the incidence of leukemia has changed but, rather,

that there
have been significant improvements in the survival rate for
children with acute lymphoblastic leukemia in particular.
Cure virtually did not occur in the early 1960s but with
each succeeding decade there have been incremental advances,
to the point where in 1990s over 80 percent of children are
surviving at 5 years from their ALL diagnosis, and most of
these children are cured.
[Slide]
Another example is the lymphomas as well. In the
1950s, there were little changes in mortality.
[Slide]
By the mid-1960s a decline in mortality rate
began, and this decline has continued into the '90s so that
from a rate of over 6/million we are now below 2/million in
terms of the mortality rate. Again, this has been achieved

by the identification of new treatments that have improved the survival rate from less than 20 percent in the early 1960s to approaching 80 percent today.

[Slide]

What have been the contributions of the NCI supported nationwide clinical trial system to improve the outcome? First, and perhaps most important, is by conducting randomized Phase III clinical trials that reliably identify superior new treatments, and I will talk about this more in a few minutes.

Second, by providing children with cancer throughout the United States and Canada with access to state-of-the-art treatment protocols that are developed by national experts, and that have multiple levels of review for scientific quality and multiple levels of

review for
13 patient safety.
14 Also, by providing central review of pathology and
15 imaging, leading to nationwide improvements in diagnosis and
16 staging, and another contribution, by supporting the
17 research studies that have led to the identification of
18 reliable clinical and biologic prognostic factors, and I
19 will come back later to talk again about the importance of
20 this.
21 [Slide]
22 First, let me emphasize the importance of
23 randomized Phase III clinical trials. Why do we put such
24 emphasis on this? One reason is because what is completely
25 logical and by all accounts should work, doesn't.

Identifying new superior treatments is an empirical and not

a deductive process.

One example comes from the cardiac literature.

Anti-arrhythmic therapy to prevent mortality from fatal

arrhythmias, and here is the logic: that elevated

ventricular premature beats are associated with early death.

Encainide and flecainide suppress ventricular premature

beats, therefore, the application of these drugs should

reduce mortality in patients with ventricular premature

beats. That is absolutely perfectly logical and is

absolutely perfectly wrong. The randomized clinical trials

supported by the National Heart, Lung and Blood Institute

demonstrated that the patients who were randomized to

receive these two drugs had higher mortality rates than the

patients randomized to receive placebo. We have to subject

-- I am not arguing that we be illogical but, rather, that we subject our logic to the empirical testing in appropriately designed clinical trials.

[Slide]

Another reason we feel so strongly about these trials is that we need reliable answers to questions of therapy. If we were to accept a more toxic therapy as superior when it really is no better than standard therapy, this would have serious consequences for future patients. We would be treating future patients with therapy that is

more toxic and they would not be receiving any benefit from that more toxic therapy. So, we need reliable answers to questions of therapy.

The conclusions that are reached from single-arm and non-randomized clinical trials often have

limited
reliability, and they have limited reliability for several
reasons. One is that apparent improvements that are
ascribed to a new treatment in a single-arm trial are often
due to patient selection. It is the patients that enter the
trial and not the treatment that are different and that
account for the apparent benefit for the new treatment.
Another reason is that the improvement that we
ascribe to our new intervention and the patients that we
have treated with our new intervention may not be due to
that but may be due to some uncontrolled factor, such as we
now have better supportive care; our surgeons are better;
our radiation oncologists are better at delivering radiation
oncology. It may be due to those changes and not to the new

19 treatment that we are evaluating, and randomization avoids
20 these problems.
21 [Slide]
22 One example of the selection bias and how it can
23 give misleading answers -- over the last decade a number of
24 single-arm trials suggested high response rates and survival
25 rates for high-dose chemotherapy in women with metastatic

1 breast cancer. At M.D. Anderson researchers looked at
2 outcome for 1600 patients with metastatic breast cancer.
3 All of these patients received conventional chemotherapy,
4 standard doses of chemotherapy agents. None received high-
5 dose chemotherapy. The patients who would have been
6 eligible for a high-dose chemotherapy protocol had higher
7 response rates and had higher survival than the patients who

were not eligible, and the recent randomized studies comparing high-dose chemotherapy for breast cancer to conventional chemotherapy have raised questions about the true contribution of this approach to the treatment of breast cancer.

[Slide]

So, what are the Phase III trials that we support, and what are their characteristics? First, the Phase III trials that we support are large trials. They are expensive trials because of their size. They require hundreds and, in some cases, over a thousand patients to reliably identify clinically meaningful differences between treatments being compared.

In our Phase III randomized trials, patients are randomized to receive what is considered best available

therapy or to receive some new treatment, and the new treatment is prioritized for evaluation based on preliminary data suggesting its potential for improving outcome, and

improving outcome could either mean better survival and, in some cases, diminished toxicity.

These trials address important questions of therapy and we don't know the answer to them. I may have my hunch a bout which arm is better, and Dr. Brown may have a different hunch about which arm is better. We truly don't know the answers to which treatment is better.

[Slide]

An important point, and Dr. Hirschfield alluded to this, in the culture of pediatric oncology research is that participation in Phase III trials is considered an appropriate standard of care for children with cancer. The rationale for this is that our standard

treatments, none of
them are perfect. They either don't have sufficient
efficacy, or they have excessive toxicity. So, for most of
our cancer types we are looking for better treatments.
Secondly, this is in the context of multiple
safeguards for patient protection, including the multiple
levels of scientific review and review for patient safety
and, of course, is in the context of appropriate informed
consent and assent.
So, given these, it is felt appropriate in most
circumstances to ask families to consider participation in
Phase III trials and historically most families have
accepted participation.

We generally have Phase III trials available for
most types of childhood cancer. There are 25 to

30 Phase
 3   III trials open at any given time for the
different types of
 4   childhood cancer.
 5   [Slide]
 6   I will describe a couple of examples
of Phase III
 7   trials that have changed standard therapy for
specific types
 8   of childhood cancer.
 9   This is an example for a pediatric
acute
10   lymphoblastic leukemia, the Children's Cancer
Group-1922

11   trial for standard risk ALL, a population that
before this
12   trial had about a 75-80 percent 5-year event-
free survival.
13   In this case, what I will be focusing on is the
comparison
14   of which steroid is the best steroid for
treating children
15   with standard risk ALL -- is it prednisone,
with half the
16   patients on the left receiving prednisone; or
is it
17   dexamethasone, with half the patients on the

right receiving
dexamethasone?

There was a second randomization as well, and that question was whether the drug 6-mercaptopurine, or 6-MP, was better by the standard oral route or whether a new way of administering that drug, intravenously, was superior?

[Slide]

The results are shown here. The two lines represent patients ID and OD, patients who received

dexamethasone, and these patients had a significantly improved outcome compared to the patients in the two lower curves, the OP and the IP curves, who received prednisone, and this established a new standard therapy for children with standard risk ALL, that dexamethasone is a preferred steroid.

Before I leave this slide, as an aside, if you compare the blue and the red lines, the blue line is the patients who received the old way of delivering 6-MP, oral 6-MP. The red is below that. It doesn't look better. The IV, the new way, wasn't better. Comparing for patients who received prednisone, again, the yellow line received the old way and the light blue line received the new way. So, what we try, what is new doesn't always work but we subject it to the test. We carried forward the dexamethasone; we discarded the IV 6-MP.

[Slide]

The other example of a randomized Phase III trial that I will present to you illustrates the concept that pediatric oncology drug development is a long-term commitment, and this example is of ifosfamide

and etoposide
22 for Ewing's sarcoma, a cancer of the bone
primarily in
23 adolescents.
24 In the mid-1980s ifosfamide was first
studied in
25 children. It was identified, as a single
agent, to have

1 activity for Ewing's sarcoma. By 1987, there
were reports
2 that the combination of ifosfamide and
etoposide, two anti-
3 cancer drugs together was very effective
against Ewing's
4 sarcoma. These were patients who had
relapsed with their
5 Ewing's sarcoma.
6 A Phase III trial was initiated
that evaluated
7 ifosfamide and etoposide for Ewing's sarcoma.
This trial
8 took a number of years to complete. By 1994
the trial
9 closed, and by 1995 the results were
available that
10 ifosfamide and etoposide improved outcome for

Ewing's
sarcoma.
[Slide]
This just shows the schematic for that study,
illustrating, again, that patients were randomized for what
was, before this trial, the best available standard therapy,
three drugs, or to those three drugs that alternated with
ifosfamide and etoposide.
[Slide]
And, the benefit for the patients receiving
ifosfamide and etoposide, 69 percent versus 50 percent, was
3-year event-free survival, and this, like the previous
study, established a new standard of therapy for children
with Ewing's sarcoma, the standard including ifosfamide and
etoposide.
But identifying this new therapy required a

commitment of resources for over a decade from the initial evaluation of ifosfamide in children to the eventual demonstration that this drug actually improved outcome for children with Ewing's sarcoma, and our systems have to be able to accommodate this long-term commitment.

[Slide]

I will just note that you have in your handout other examples of recent Phase III trials that have made important findings in the treatment of children with cancer.

[Slide]

Also, in your handout you have ongoing or, in one case, soon to be initiated trials of really important questions of therapy that over the next 1-5 or perhaps longer years will answer these important questions of therapy for children with Hodgkin's disease or

T-cell ALL or
16 neuroblastoma.
17 [Slide]
18 This is what we strive for in our system of Phase
19 III trials. This slide shows outcome for children with
20 acute lymphoblastic leukemia treated on sequential series of
21 clinical trials in the Children's Cancer Group from the late
22 1960s up through the 1990s. Each series of clinical trials
23 involved hundred and more recently thousands of patients,
24 going from one series of clinical trials to the next,
25 building on what worked in the previous trials, discarding

1 what didn't work and having ever increasing survival rates
2 for children with ALL. This is really what we strive for,
3 for all of the childhood cancer types.
4 [Slide]
5 An important concept in pediatric

oncology is the
6 concept of risk-adjusted therapy, that is, classifying
7 patients by prognosis. This slide shows a patient
8 population for which the survival rate is approximately 70
9 percent, and our approach to treating this patient
10 population and designing clinical trials for this population
11 would be based on the 70 percent survival rate, and the risk
12 and the types of new treatments we would evaluate would be
13 based on this.
14 [Slide]
15 However, ifosfamide we could identify factors that
16 allowed us to determine which patients do well with current
17 therapy and which patients do poorly with current therapy,
18 essentially to split that first group into two groups, a
19 group that does poorly with the current treatments that we

have and the groups that do quite well with the current treatments that we have, then this would be very helpful in terms of increasing the efficiency with which we can identify better treatments.

[Slide]

The patients who have low survival rates with

current treatments are the ones that may well benefit from novel, more aggressive therapeutic approaches that are associated with greater risk, and the patients with very good outcome with current therapy should be spared more intensive and toxic treatments and, indeed, we may focus our research efforts on minimizing acute and long-term toxicities for these patients.

[Slide]

In order to use risk-adjusted therapy, this

requires that we determine reliable prognostic factors for determining which patients do well and which patients don't with current therapy. To do this requires analyzing outcome for larger numbers of patients, preferably treated in a uniform manner. Since biology is so improvement in determining prognosis for these biological prognostic factors, it requires collection and analysis of tumor tissue.

The protocol-treated patients in the Cooperative Group tumor banks have been invaluable in identifying and confirming these prognostic factors that we now use to assign treatments for children with cancer.

[Slide]

So, let me take a few minutes now to describe what this research infrastructure is that supported these Phase

25 III trials, that supported the identification of prognostic

1 factors to support risk-adjusted therapy.

2 In terms of the scope, approximately 5000 children

3 are entered each year onto treatment trials supported by the

4 National Cancer Institute. The majority of these are

5 entering Phase III trials but we also have entries onto

6 Phase II trials to identify activity of new agents and Phase

7 I trials to identify safe doses of new agents. For the

8 tumor types listed here, ALL, acute myeloid leukemia, Wilms'

9 tumor -- for some of these, most of the children diagnosed

10 with these cancer types in the U.S. and Canada will be

11 entered onto one of the NCI-sponsored clinical trials.

12 [Slide]

13 These trials are supported through the Cooperative

Groups. Historically, these have been the Children's Cancer Group, the Pediatric Oncology Group, a group for rhabdomyosarcoma and Wilms' tumor. Together, these represent over 200 institutions throughout the U.S. and Canada, banding together to development research protocols for children with cancer, and it represents most of the institutions that treat children with cancer.

I would add that in addition to the pediatric groups here, we support the Pediatric Brain Tumor Consortium, specifically focused on developing new treatments for pediatric brain tumors; a neuroblastoma consortium for focusing on new treatments for neuroblastoma;

as well, a number of investigator-initiated projects and program projects, for example at St. Jude's Children Research Hospital.

[Slide]

In terms of the Cooperative Group structure, the four historical groups are now merged into a single entity, the Children's Oncology Group, and the decision to do this was based on improving the efficiency and developing and conducting clinical trials to identify better treatments for children with cancer.

[Slide]

An important characteristic of the clinical trials program is its multi-modality. To treat children with cancer requires specialists from many different areas and these must all be a part of the research system, including the pediatric hematologist, oncologist, the surgical subspecialist, radiation oncologist, pathologist, laboratory researchers, nurses, epidemiologist, radiologist and the

clinical research associates, and others.

[Slide]

To do this work, to have 5000 children entering clinical trials each year requires a commitment to infrastructure. This infrastructure includes an operations office involved in the administration of these trials, coordinating protocol and development and distribution. It

involves the statistical center for the statistical design of protocols for data collection.

[Slide]

Of course, it requires the support of the member institutions in supporting the investigators at the institution, the clinical research associates for collecting data, and currently we provide approximately $1700 to institutions for patients entered that partially reimburses the research cost to enter patients on these

clinical
trials. It requires support for tissue collection so that
we are able to do biology studies, and support for
submitting things like radiographs and pathology specimens.
[Slide]
Then, there are the groups that actual do the
science, that develop the clinical trials, the disease and
discipline committees -- disease committees for all of the
different tumor types, discipline committees for surgery,
radiation oncology, the disciplines involved in treating
children with cancer, and then individual study committees
that design and implement each of the individual clinical
trials.
[Slide]
In addition to this commitment to ongoing support
of Phase III trials, we also recognize our

responsibility to
25 survivors of childhood cancer. Survivors are at risk for

1 long-term sequelae of therapy depending on their diagnosis,
2 depending on the type of cancer that they had that could
3 involve the heart or lungs; that could involve second
4 cancers; impaired fertility effects among offspring, central
5 nervous system dysfunction, and so on.
6 [Slide]
7 In part, to support research to identify these
8 long-term effects and to identify ways to either prevent or
9 ameliorate these, we support the Childhood Cancer Survivor
10 Study. This is a retrospective cohort involving 13,000 5-
11 year survivors of childhood cancer who are surveyed for
12 their long-term health and psychosocial status.
13 [Slide]
14 The Childhood Cancer Survivor Study is

currently
15 addressing important questions for survivors, looking at the
16 late mortality risk for survivors, looking at second cancers
17 developing and what the risks of second cancers are, looking
18 at pregnancy outcomes after treatment for childhood or
19 adolescent cancer, looking for cancer in offspring of
20 pediatric cancer patients, and following thyroid disease and
21 survivors of childhood Hodgkin's disease, and then looking
22 at smoking and other health-associated behaviors among
23 survivors of childhood cancer.
24 [Slide]
25 Let me spend the last few minutes talking about

1 unmet needs and looking towards the future. In spite of the
2 progress that we have achieved over the past four decades,
3 there are still over 2000 children and

adolescents who die
each year from cancer in the United States.

Some of the children who are cured with our
current treatments experience diminished quality of life
because of long-term effects of their cancer diagnosis and
treatment, and our current therapies for many cancers are
near-maximal intensity and we need new treatment strategies
to improve outcome for these children.

[Slide]

This shows the distribution of cancer mortality in
children younger than 20. About a third of the deaths
result from leukemia, about a fourth from brain tumor.
Endocrine is actually neuroblastoma, and so on. We need
better treatments, new treatment approaches in each of these
different cancer types.

[Slide]

The handout has some of the different

approaches

that we are trying for some of these different diagnoses.

What I will focus on in these last few minutes is that we are moving towards a new era in treating cancer both in adults and children, and an era in which our treatments are molecularly targeted and the treatments are based on specific molecular characteristics of the cancer. The

treatments that we have had to date have been, in large measure, are non-specific treatments that harm normal cells and cancer cells as well. These treatments, in principle, will be more specific for processes required for tumor cell survival and growth but, as I mentioned early in the talk, what is perfectly logical and makes perfect sense may not be true and, of course, we will have to evaluate

rigorously
whether these new treatments actually do work for children
with chancer.
[Slide]
There are a number of opportunities for
molecularly targeted therapies. The example that I will
focus on is for Philadelphia chromosome positive ALL, but
there are also opportunities using monoclonal antibodies and
opportunities using growth factor receptor inhibitors.
[Slide]
This example -- Philadelphia positive ALL, is ALL
that develops because of a fusion protein resulting from
chromosomal translocation. This has very poor outcome with
our treatments, 20 or 30 percent event-free survival.
This fusion protein that causes the leukemia has
an enzyme activity that is absolutely essential

for the
23 leukemogenic effect of the translocation, and we
now have a
24 drug, STI571, that is an inhibitor of this
critical enzyme
25 activity. This drug inhibits the proliferation
of the

1 leukemia cells and induces them to undergo
apoptosis or cell
2 death.
3 [Slide]
4 This schematically illustrates the
genetic change
5 in the Philadelphia chromosome positive ALL
with the 922
6 translocation leading to the leukemogenic
fusion protein
7 that produces a Ph positive ALL. Over, on
the right, is
8 what happens when STI571 inhibits the activity
of the fusion
9 protein and causes the leukemia cells to die,
resulting in
10 restored normal hematopoiesis.
11 [Slide]
12 Phase I trials have been completed in
adults with

chronic myeloid leukemia. High levels of anti-leukemia activity were observed. Pediatric Phase I trials are ongoing and will be completed shortly. And, we are working with the Cooperative Groups to develop a pilot study for newly diagnosed patients to incorporate STI571 with conventional drugs to treat these patients with a type of ALL that currently, with current therapy, has such a poor prognosis.

[Slide]

In closing, let me first emphasize that the public health of children has been improved by the long-term sustained NIH support of this ongoing infrastructure for conducting clinical research for children with cancer. As a

result of this long-term sustained NIH support, superior new

treatments have been identified, identified based on definitive and reliable evidence, and these new treatments, and superior treatments, have been made widely available to children with cancer throughout the United States and Canada.

[Slide]

The second point I would emphasize is that progress in the past as well as progress in the future depends on collaboration and cooperation among the pediatric cancer researchers and healthcare professionals throughout the country working together. It depends on the families and their advocates participating in these trials. It depends on the National Cancer Institute recognizing that this is a priority area. It depends on the academic and pharmaceutical developers of new cancer

treatments and on
17 the FDA and its regulations. And, it depends on third-party
18 payers supporting the clinical care costs for treating
19 children with cancer, and then all of these groups working
20 together, so that the most promising therapeutic approaches
21 are expeditiously evaluated with the ultimate objective of
22 continuing to see improvements in outcome for children with
23 cancer.
24 I thank you and I would be glad to address any
25 questions that you have. Thanks.

1 DR. CHESNEY: Thank you very, very much, Dr.
2 Smith. That was an exceptionally complete and informative
3 overview. Let me just ask Dr. Hirschfield, should we accept
4 questions now or wait until after the break? Now? Are
5 there any questions? Yes, Dr. Fink?

DR. FINK: Apropos yesterday's discussion, your data on Ewing's sarcoma showed a p value of less than 0.00005. Was there a data and safety monitoring board in place that could have led to earlier termination of that study and let more children receive the optimal therapy?

DR. SMITH: Yes, for all of our trials we have data and safety monitoring committees. The Children's Cancer Group, the Pediatric Oncology Group have data and safety monitoring committees that are looking at the interim results from our Phase III trials, and the protocols are written with guidelines for what the monitoring boundaries should be for these trials.

I wasn't a member of the data monitoring committee for that trial so I don't know the specifics for that trial,

I can remember in the past few years a number of trials that have closed either for one arm being superior to the other arm or closed because there was no chance that a difference could emerge related to the question being addressed. We have described our data monitoring committee system in the Journal of Clinical Oncology and I would be glad to provide you with that reference.

DR. KRAILO: Mark Krailo, from the Children's Oncology Group. There was a data monitoring safety board for that study. We met three times while the trial was ongoing, and the differences in the therapies emerged later on in this trial. So, they emerged after the study had completed all its accrual.

DR. CHESNEY: Are there any other questions for

Dr. Smith?

[No response]

Thank you again. As Dr. Smith pointed out, the role of families as advocates for children is so important in all studies but particularly in oncology studies, and we are very fortunate this morning to have Dr. Susan Weiner, from the Children's Cause, who will speak to us on lessons and challenges of participation in clinical trials, a family perspective.

Lessons and Challenges of Participation in Clinical Trials -- a Family Perspective

DR. WEINER: Thank you, Dr. Chesney and Dr. Santana, for giving me an opportunity to speak this morning, and we are grateful -- I figure in my next life I will use Power Point but, somehow, in my generation it hasn't quite caught on -- we are specially grateful in the

parent
25 community for the increased attention that the FDA has been

paying to pediatric cancer under the leadership of Drs. Pazdur and Hirschfield.

As some of you know, I was the parent of a child with a brain tumor who was diagnosed in infancy and died just short of his fourteenth birthday. Since then I have worked as a patient advocate in the brain tumor community and in the pediatric cancer advocacy community, building programs to serve patients and counseling hundreds of families who are trying to make rational decisions about treatment and care in an irrational situation. I have founded the Children's Cause to devote more time to strengthening the pediatric cancer community through education and advocacy.

The experience of children and families who struggle with the diagnosis of childhood cancer is different from that of other pediatric diseases and disabilities. When I watched my son years ago in a special education class interact with his class mates disabled as a result of a variety of other diseases, I realized the uniqueness of his experience and that of our family. While they lived the slow course of chronic illness and developmental disabilities, we were living with an internal anti-personnel bomb. The uniqueness of the pediatric cancer experience lies not in its threat of its incidence or as a public health menace but, rather, in its uniquely destructive force

on children and families.

The uniqueness of pediatric cancer, of course, is

inherent also in its diversity, namely that it represents many orphan diseases, often of embryonic origin. Families affected by childhood cancer share a common goal with the pediatric oncology research community. We want new treatments that are less toxic, that can destroy disease and spare healthy tissue with laser-like precision. Despite extraordinary gains in the treatment of some childhood cancers, many other childhood cancers, most notably solid tumors and, of course, brain tumors, have not enjoyed the same degree of improvement. We are still a long way from achieving our goal.

Our question as parents and patient advocates now is what will it take to ensure that pediatric oncology researchers can have rapid access to new agents so that our

children with cancer can receive what so many people call the best possible treatment? During the 1990s, FDA and Congress, urged on primarily by the American Academy of Pediatrics, created initiatives to generate pediatric information on new and improved oncology drugs for purposes of labeling, as well as to increase industry financed pediatric research.

For children with cancer, both the Pediatric Rule and the pediatric exclusivity provision of FDAMA have had

disappointing results. While it has been successful for other diseases, the interpretation of FDAMA has resulted in relatively little pharmaceutical investment for our children. Now FDA's emphasis for labeling for pediatric oncology drugs, by enforcing the Pediatric Rule,

leaves a
 6   series of questions about whether this
enforcement will slow
 7   and alter the course of pediatric cancer
research, questions
 8   which I hope we will discuss later today.
 9   First, how can strict requirements for
labeling
10   possibly keep pace with rapid advances and
knowledge about
11   gene expression and molecular targeting?
12   Will the enforcement of the rule, in
effect,
13   redirect the strategy of the cooperative
groups that have
14   been responsible for the successes in children
cancer
15   treatment from consensus development and layers
of review in
16   clinical trials using available drugs off-label
that
17   pediatric oncology researchers believe are the
most
18   promising approaches?
19   Finally, why should research
priorities in
20   pediatric oncology now be shaped by a regulatory

requirement
21 that places first those diseases that may be judged the same
22 or similar in adults as in children?
23 As parents and patient advocates, we want clinical
24 research studies in children with cancer to be determined by
25 the medical need to answer the most important research

1 questions and, of course, by the most promising scientific
2 opportunities, and not by ill-fitting regulatory
3 requirements.
4 Neither FDAMA nor the Pediatric Rule offer
5 successful solutions to achieving the goals we all share for
6 children with cancer. We seem to have strayed from our
7 point. We have not yet struck the right balance between
8 incentives and enforcement in pediatric oncology research.
9 We should use industry's desire for exclusivity to encourage

them to invest in pediatric oncology research and, at the same time, expect conforming to academic standards and strict cooperation with the cooperative groups. From the FDA, while we depend on your watchfulness, there needs to be a more flexible approach to regulation in pediatric cancer, and when it is time to re-authorize FDAMA we may need to craft special provisions appropriate to pediatric cancer research.

If rapid advancements in basic science are to translate into effective treatments for our children in the foreseeable future, a new interactive paradigm is needed whereby each constituency involved in pediatric oncology research will need to show more flexibility, a greater commitment of resources and a continuing awareness of the

uniqueness of our diseases. Thank you.

DR. CHESNEY: Thank you very much for articulating

the issues so clearly. Are there questions for Dr. Weiner?

DR. HIRSCHFIELD: I would like to ask if there are any perspectives you would like to share with regard to family participation in the process?

DR. WEINER: Could you be a little bit more specific?

DR. HIRSCHFIELD: We have all stated that research is the standard of care, and it is a different paradigm when a child has cancer than going to the local pediatrician and getting whatever the standard of care may be for that particular community. It is a process where one has to sign consent forms, be made aware of protocols, and learn a new vocabulary, and I would like to know if you

would make some
14 comments with regard to these aspects which are different
15 than families have when they are treated typically for other
16 illnesses.
17 DR. WEINER: There are two things that I think are
18 operating now. One is that there is a great reliance on the
19 wisdom and the necessity of referral to centers of
20 excellence to be treated. And, when families line up in a
21 pediatric neuro-oncology setting, there is an important kind
22 of bonding that takes place initially. There is an enormous
23 need to assimilate a great deal of information under very,
24 very dire circumstances. I believe that parents are helped
25 these days by the web, by the free and open availability of

1 medical information from reliable sources such as the NCI
2 and the FDA.

As every pediatric nurse knows, there is an initial phase of sort of being deaf, dumb and blind at the beginning and it is during that period where consent typically has to be signed over a period of days or understanding what needs to be done, and we are very much dependent on the good will and directness of the medical team. Does that answer your question, Dr. Hirschfield? No?

DR. HIRSCHFIELD: Well, you have not only had your own experience but the experience of talking to hundreds of other families, and I wanted our colleagues to be able to have a little better understanding of the impact of having the diagnosis of a child with cancer on not just the type of care but on the lives of the families.

DR. WEINER: Well, it is a life-altering situation

and many families are, of cost, cast in disarray. The siblings are oftentimes neglected, and work is sometimes entirely neglected. There is a sense of unreality about being in a hospital and not being in a hospital at the same time. That is, while the hospital environment is a menacing phase, one relinquishes the care to strangers on the one hand. On the other hand, being out of the hospital means that life should appear normal which, of course, it is never again since a diagnosis of life-threatening illness means

that there is always imminent danger.

Does that do it? Let me try again?

DR. HIRSCHFIELD: I think you have shared some important information. Would you just elaborate a little bit more on what types of supports and what types of crises

are faced, and where do people turn when they face these crises? Is it to the medical system? Is it to each other? Or, what are the responses and what are the resources available?

DR. WEINER: Well, there are many pediatric groups that have formed support groups and produce information materials but that typically is not accessible at the time of diagnosis. That usually comes after consent is signed and after the first treatment decision is made. It is often most accessible at the point of occurrence.

But with the Internet there are increasing resources that are out there. There are chat rooms, and for whatever they are worth, they represent a community. There is no substitute for the experience of one parent with another, and it is very important for children's

hospitals
and medical settings to offer that opportunity.
Finally, I think, you know, in terms of management
of the sort you are referring to, it is very important to
ameliorate -- it is difficult for me to describe the degree
of distress. It is very important to have an intermediary

between the pediatric oncologist and the family -- not a
research nurse, a nurse practitioner.
I guess I would like to leave this part of the
conversation with something that I have recently called the
"parents' double-bind," the parents of children with
cancer. That really amounts to a situation in which the
diagnosis of cancer as a life-threatening disease really
violates the first principle of being a parent, that is, you
have failed to protect your child from disease

and imminent
death. However, in order to ameliorate that diagnosis you
have to relinquish your role as parent and fail to protect
your child from harmful and sometimes toxic treatments at
the hands of strangers. So, in that situation you can't
maintain your role as a parent either originally or through
treatment, and it is an understanding of that kind of
paradox that is very important and really is unique to
participating in clinical trials.

DR. CHESNEY: We do have some other questions for
you, Dr. Weiner, if you would like to stay at the
microphone. Dr. Santana?

DR. SANTANA: Susan, you made a comment that has
been resonating in my brain for a little while, and I would
like you to help me by giving examples or sharing your

24 thoughts further, and it is this concern that you have that
25 with new regulatory issues coming from the FDA as regards

1 pediatrics whether we will have to redirect the model of
2 cooperative group research and how this potentially could
3 impact it. Could you elaborate on that?
4 DR. WEINER: Well, Jim Boyett and were sort of
5 talking about this a bit yesterday. It would seem perhaps
6 unfortunate if there were studies -- let me start over
7 again, there is a paucity of subjects available in pediatric
8 oncology research. They are a valuable commodity and
9 prioritization of approaches is something that is, as you
10 know, critical towards progress. Dr. Smith described how
11 long it takes to come up with a Phase III standard of care.
12 It would be, I believe, unfortunate if these

resources
13 through the cooperative groups were to be used to establish
14 similarity equivalence of disease rather than really taking
15 account of scientific opportunity that perhaps looked more
16 promising for new treatments. That is the context.
17 DR. CHESNEY: Dr. Kauffman?
18 DR. KAUFFMAN: I wanted to follow it up to try to
19 understand better if you have any specific suggestions how
20 changes in FDAMA might -- if it is renewed and if it is
21 possible to make changes. In our discussions last February,
22 as I recall, the issue came up that maybe FDAMA is not an
23 appropriate vehicle to accomplish what we want to
24 accomplish, and there are some inherent characteristics of
25 the current law that make that so.

1 One is that many of the drugs that

need to be
studied in kids, usually in combination, no longer have
exclusivity to which to attach the benefits of FDAMA. So,
FDAMA is irrelevant to those drugs.
Secondarily, of the new drugs, new agents, they
don't have the market size where FDAMA has had the most
impact -- they just don't have the market size to bring
FDAMA into play. So, what do you see as concrete changes in
the law that might help with the oncology agents for
children?
DR. WEINER: Well, you know, I am not an attorney
and not someone who really is experienced in crafting the
concept-precise proposals that you are aiming at, however,
one suggestion that came up in discussion yesterday
afternoon might be the point that the six months of

exclusivity is more valuable -- you know, somehow or other, the older the drug, the closer it is to going off patent, the more likely it is that those six months are likely to be valuable. So, in some sense, FDAMA might take account of the kind of history or newness of the drug, and how that could be crafted I am not prepared to say right now, but the phrase "sliding scale" has been used a lot but the exact dimensions of that remain to be seen.

DR. CHESNEY: Dr. Nelson, you had a question?

DR. NELSON: Thank you, and thank you for your

remarks. When you started talking about the double-bind it began to address the area I was interested in asking about, which is specifically the consent process.

One of the things that is explored in the process

of looking at informed consent is the ability of an individual to distinguish research from standard of care but, yet, we are in the process of conflicting that distinction by saying that the standard of care is to participate in research. So, I am just interested in hearing your reflections about how at some time in the process a parent becomes aware of the research components, and what suggestions you might have or directions for looking at the quality of the information and the quality of the decision that a parent makes to enroll in that kind of a process.

DR. WEINER: This is, of course, the heart of the matter. As those of us who are in the pediatric oncology community really know in our heart of hearts, parents do not

make that distinction. It is in some sense unthinkable and many of us can report instances in which the most sophisticated parents and family members will say, after a course of treatment and after having signed consent, that their child was not part of a research study. I think that that is evidence for the kind of power of the need to believe that one is treating one's child, one is subjecting

one's child to harmful intrusions for the purpose of their getting better.

There may be other ways around that. The consent form, and as many of you have reviewed dozens of these -- the consent form language is always contorted in a way that makes it difficult. That can always be tinkered with. Sometimes, particularly for example in Phase I

trials, it is
useful to have the investigator and the physician care-taker
roles distinguished between people. I think there is no
easy solution but those are some of the strategies.

DR. CHESNEY: Dr. Murphy?

DR. MURPHY: Susan, you were at our February meeting so you know that many of these issues were brought up and we thought that we left that meeting with a way to resolve many of these issues. And, Dr. Pazdur is, you know, going to be presenting the guidance outcomes for the group here and the approach, and after he speaks and presents the process to the group I think it would be helpful for us to hear where you still think there are issues, particularly as relates to the selection of products to be driven by science, because that is the very concern we

have, that
22 FDAMA be driven by science and not because there is a lot of
23 money to be made off of a block-buster product.
24 And, the second issue is flexibility and that is
25 one of the goals of this approach, to provide flexibility

1 for the development of pediatric oncology products while not
2 making it a complete free for all. By that, I mean that
3 every group ends up with administering things in a
4 regulatory way and in a different way.
5 So, I would just like to say I would like you,
6 after we hear Dr. Pazdur, to point out to us where you think
7 this approach does not address those two issues in
8 particular because I think one of the concerns we have at
9 FDA is, as Dr. Smith has clearly articulated this morning,
10 that there has been a lot of success in this

field because
of the cooperative groups and the standard of care, and we
don't want unintended results here where FDAMA drives the
process in a different direction. So, we don't want to
disrupt something that is working. I guess that is one of
our concerns, we keep moving in this area. So, again, those
two issues, the flexibility and why this process won't help
that and why this process won't help the science approach,
would be questions I would ask you to come back and tell us.
Okay? Thank you.

DR. CHESNEY: Our next speaker is Dr. Richard
Pazdur, who is Director of the Division of Oncology Drug
Products at the FDA, and he will speak on the FDA
initiatives in pediatric oncology -- adaptation of the
general case to special circumstances.

FDA Initiatives in Pediatric Oncology

Adaptation of the General Case to Special Circumstances

DR. PAZDUR: Good morning. I somehow feel like a fish out of water. I am not a pediatrician and I was thinking back on my pediatric experience and, I am ashamed to say, it has been about 25 years ago that I treated a pediatric patient. So, if I make any major faux pas in the science and medicine of pediatrics, please forgive me.

[Slide]

I came to the agency about a year ago. In fact, the last week in September will be my one-year anniversary as far as starting at the FDA. My former job was as a clinical professor at M.D. Anderson Cancer Center where I was very involved with Phase I, Phase II and Phase III drug development in colorectal carcinoma, a quite different

disease than one would see in pediatrics. Nevertheless, in my experience in interacting with my colleagues in pediatrics at M.D. Anderson and in the greater Houston area, I was always aware of a particular angst or a particular distress that the pediatric oncologist had when we talked about clinical trials, especially when the adult medical oncologist had a wide array of new agents that they were studying. There was somewhat of an uncomfortable feeling among the pediatric oncologists that they simply were not getting those good drugs right away. In other words, they were somewhat relegated almost to a second-class citizen --

let's see how these drugs work in the adults and they maybe we will consider developing them in pediatrics.

When I got to the agency, it was clear

from
Dianne's presentation and working with the pediatricians in

our oncology group that the implementation of the FDAMA

incentive program was simply not working in oncology, and I

kind of stepped back because I was new and that always gives

you a fresh perspective -- right? -- and I said, well, why

isn't this working? And, I said, really, you have to have a

whole plan of basically developing a drug in pediatric

oncology.

When one takes a look at the applications that

come into our division of medical drugs, where are sponsors

developing drugs? They are developing drugs in the big

markets for oncology drugs -- breast cancer, prostate

cancer, colorectal cancer, lung cancer. Very few approaches

or very few applications are coming in for

indications where
18 we would even think of extrapolating from an adult
19 indication to a pediatric indication. It is very hard to
20 make that bridge between developing a drug in colon cancer
21 and saying, well, we now have to exert the Pediatric Rule
22 for development of this drug in pediatrics.
23 So, there are some very unique characteristics
24 about the whole field of pediatric oncology that I thought
25 needed revision. The difficulty in extrapolating adult

1 indications to the pediatric population in oncology is one
2 that we will discuss this afternoon, and it is a very
3 difficult decision and perhaps, as science progresses and we
4 learn more about the biology of the diseases, we will have a
5 greater flexibility in applying this rule.
6 But, as I stated before, the major

disease
7 categories that we receive applications for are in the
8 common adult malignancies which makes the application of the
9 Pediatric Rule very difficult. Nevertheless, we know that
10 pediatrics has very special characteristics both in the
11 pediatric community in general and in the oncology
12 community, and we must be cognizant of these special
13 characteristics as we develop any plan in developing
14 pediatric oncology drugs. And what are those special
15 characteristics?
16 Number one, as has been stated repeatedly, it is
17 the standard of care for patients, children, to participate
18 in pediatric protocols. I wish I could say that about adult
19 malignancies. In essence, with adults it is just the
20 opposite. It is the exceptional patient that

participates
in a clinical protocol.

Secondly, and most important, it is the relationship that the academic and the practicing pediatric oncologist has with the NCI and the Pediatric Oncology Group structure that must be protected, and that was part of a

whole development plan that we have initiated, that we do not disrupt this relationship because it has worked; it has turned pediatrics really into a very successful model of producing curative therapies in our generation.

So, in any implementation of any plan, I want to make it quite clear we are not attempting to exert a regulatory hammer on a near-perfect relationship that exists between the cooperative group structure, investigators and the NCI. The scientific agenda must be

established by the
physicians that are doing the trials, those that are
involved in the cooperative groups. We are here as a
facilitator to get those drugs, to use "regulatory pressure"
via FDAMA regulations, to act as a funnel to get those new
agents into the pediatric structure. It is not our decision
of what drugs should be studied. That should be left up to
the experts in pediatrics.
[Slide]
This is the Food and Drug Modernization Act of
1997, and this is what we call the incentive program. Some
people call it the carrot in contrast to the stick, which is
the rule, and it is a provision for a 6-month extension to
the existing marketing exclusivity or patent protection of
the entire line, and it can be granted to an entire product

line of an active moiety for providing new pediatric information that will benefit public health. The

submissions must come in response to an FDA written request, and I will go over this in a little more detail.

[Slide]

This slide provides you the Pediatric Rule, which I think you all have been briefed on as far as the membership of this committee yesterday. In this rule, this is what we kind of refer to as the stick or a mandate, and it provides that a product under review must provide pediatric information if the indication under review is a disease found in children. If a disease is not found in children a waiver may be granted. And, this is one of the major problems that we have with the application of the

Pediatric Rule, that we issue far more many waivers than we implement this rule simply because many of the diseases, or I should say most of the applications and products are being developed in common adult malignancies that do not have this ability to extrapolate into pediatric indications.

[Slide]

Most people or many people have difficulty in comparing the FDAMA incentive versus the Pediatric Rule, and what I have attempted to do in this slide is to provide you a listing or a comparison of FDAMA versus the Pediatric Rule. FDAMA is a voluntary program. It applies to the entire product line, the incentive does. There is no restriction on eligible pediatric diseases. It only applies when there is an underlying patent or exclusivity

protection. Obviously, you need something to extend.

Biologicals and some other products are excluded and orphan drugs are included.

In contrast to the FDAMA, the 1998 Pediatric Rule has the following characteristics, and these include that it is mandatory if the disease is found in adults and children, it must be studied in children. It only applies to the product and the indication under the review rather than to the entire product line, and it only applies if the pediatric disease is similar to the adult disease. It applies to biologics, and orphan products are excluded.

[Slide]

This gives you an indication of how pediatric exclusivity comes into being the actual process of how the FDA works with this. A proposed pediatric

study request is
17 usually generated. Who can generate this
pediatric study
18 request? Virtually anyone. It could be a
cooperative
19 group; it could be an academic; it could be a
commercial
20 sponsor; it could be any other interested
third party. A
21 written request is then generated from the
FDA. This
22 written request is very important because it
has the exact
23 specifics that must be followed, and these
specifics must be
24 followed to the detail to allow granting of the
eventual
25 exclusivity.

1 So, in response to a proposed
pediatric study
2 request, a written request is generated from
the FDA. A
3 sponsor, if they are willing to do it --
remember, this
4 program is voluntary -- submits study
reports after

completing the required studies and then the FDA determines, as it would in any review of an application, the scientific validity of the material that is submitted to determine whether it meets the specifics of the written request that is generated from the FDA. Because we have had a paucity of proposed pediatric study requests, we have taken the initiative to generate some written requests on our own from the Division level of Oncology Drug Products recently.

[Slide]

Let me give you the idea or the concept of this pediatric plan that we are asking you to consider here and to comment on. As I stated before, if somebody is developing a drug in an adult indication, such as breast cancer or such as prostate cancer, it is going to be hard to

say where do I go with this drug in pediatrics. It requires really, if you take a step backward, a whole plan to develop this drug.

One has to take a look at the dose in pediatrics, the toxicities in children that might be unique. What pediatric disease do you study it in? Well, there might be some diseases that may be applicable if you know a specific,

for example, genetic mutation such as in the STI drug that Dr. Smith referred to. However, for the vast majority of cases we are dealing in an area where we don't know what pediatric disease this may work into. So, therefore, you would need some type of screening Phase II study to determine the eventual activity of the drug, if it does have activity.

This is a very risky process and we are aware of this, and this whole plan that we are devising is some way of sharing the risk of developing an entire oncology drug for pediatrics with the sponsor. So, the following provisions have been made: An overview, dosing and pharmacokinetics in the Phase I one study must be done. We need this information obviously to proceed further. What is the dose of the drug? What are the toxicities?

Then, Phase II or pilot studies in a range of potential indications can be performed, and these are usually stipulated in the letter or there is some flexibility and here, again, we would encourage strongly sponsors or people that have received a written request to discuss what Phase II studies they want to do with the

pediatric academic/cooperative group community. Pediatric patients are an important national resources. We do not want them to be used as a commodity. They should be used i the best -- and I shouldn't even use the word "used" but

they should participate in the best designed scientific studies, designed to ask the most important questions.

Here, again, this plan is to introduce either old agents that have not bee studies, and by old agents I mean approved drugs in oncology, or new molecular entities that have not been approved yet by the FDA. It is important to note that this development plan is not a supplemental NDA since efficacy does not necessarily need to be demonstrated. Obviously, we would want efficacy to be demonstrated if the

drug is active and for us to label this drug as well as to approve this drug for a pediatric indication if warranted. This applies to both new agents and approved agents that have not been adequately investigated in pediatric oncology.

[Slide]

Let's take a look at the first stage of development, and this correlates basically with a classical Phase I study in medical oncology or pediatric oncology. Phase I studies would be done to determine the dose, the pharmacokinetics and the toxicities -- pretty straightforward. Roughly, about 25 patients would be planned to be entered, and here again we have some flexibility. Obviously, nobody knows a priori, before starting the study, exactly how many patients would be

entered on a Phase I study. So, there would be a range here and some flexibility.

The important point here is if unacceptable toxicity occurs the development would stop and an exclusivity extension would be granted -- pretty generous, right? The reason behind this is we look at this as an exceptional situation. We feel that there would be very, very, very, very few drugs that would go to Phase I in pediatrics and would be stopped because of unacceptable toxicity. Nevertheless, if somebody makes a good faith effort in developing this drug and proceeding with a development plan to a point where they can no longer proceed, then we believe that this has been a good faith effort and, therefore, they should be rewarded by the

granting of exclusivity. We view this as a very generous concession, in a sense, but we realize this is an important aspect to promote and act as a funnel of getting new drugs to the pediatric oncology community.

The most important aspect, rather than concentrating on an exception, is where we believe most of the drugs will go, and that is if the toxicity is acceptable, and here, again, that is a decision that will be made by the pediatric, academic and cooperative group community, the development of this drug should proceed to a second stage and this is the vast majority of cases, and let's go on to that second stage.

[Slide]

Here, again, it is rather general because we cannot dictate specific situations to a general

plan such as
this, what we are looking for in our Phase II studies is
what is the activity of this new molecular agent or an
existing approved agent in pediatric malignancies? So, we
would propose that Phase II studies would be done and here,
again, it would depend on what disease one is studying. If
it was a very refractory situation one could take a look at
single agents. Perhaps we would take a look at window
studies, perhaps at add-on studies or pilot studies of
various combinations to demonstrate an agent's
characteristic and contribution to the following --
efficacy, perhaps using surrogate endpoints such as response
rates, such as time to progression, and this would also
provide justification for further development to examine
clinical benefit.

[Slide]

Possible outcomes after the Phase II portion -- well, if efficacy is demonstrated on the basis of a surrogate endpoint, this may lead to a concept known as accelerated approval or subpart (h), and for those of you who are unfamiliar with this FDA provision, it allows us to approve drugs on the basis of a surrogate endpoint such as response rate, such as time to progression, with an approval for marketing with a commitment that a clinical benefit such as a survival benefit or a palliative benefit in terms of symptoms be subsequently studied in a Phase IV commitment. But, anyway, if efficacy is demonstrated there is a possibility for accelerated approval, allowing for full marketing of the drug.

If there is no beneficial effect that is observed, then the development is halted and stopped. The drug simply doesn't work. Here, again, a good faith effort has been made in the development of this drug and even if the Phase II studies are what we would call negative in that they have not shown anti-tumor activity in a particular disease to warrant further development, exclusivity would be granted on this attempt to provide further information.

We would hope the latter or the third portion is the most common one, and that is if results are promising but not sufficient to support approval a commitment to further development would be made. As stated here, in all three cases granting of exclusivity extension can be made. It is important. We are interested in good

quality data.

The granting of exclusivity on "negative" data whether it be a negative Phase I study with prohibitive toxicity or with negative clinical results does not mean that we are accepting poor quality data, studies that are poorly conducted. We are interested in working with the cooperative groups to guarantee the best scientific

integrity of the studies, and we will be looking quite closely at how these studies are performed in our review process.

[Slide]

The results of the completion of a pediatric development plan are listed here. The results are summarized in a study report and submitted to the FDA where a determination based on meeting the proposal is

finalized.

Upon review, if the conditions of the initial written request are met, regardless of outcome, a 6-month exclusivity extension may be granted. We are looking for well designed, well executed studies where negative results can qualify as long as these studies are well designed and well executed. Our intent is a prospective plan to produce and to really introduce new information of importance to the pediatric oncology community.

In the year I have been here, although as I have stated before I am not a pediatrician, because of Dianne's influence and because of Steve's influence, it has been on our radar screen to make pediatric oncology an important element at the FDA. Not only have we written this plan up in a guidance, which is on our web site and I

would
23 encourage all of you that are interested
to view that
24 guidance, but also we have taken an active
recruitment
25 posture as far as recruiting two
additional pediatric

1 oncologists to our review staff. We have 20
medical
2 oncologists, three of which are pediatric
oncologists,
3 really to underscore our commitment to the
pediatric
4 oncology community in developing drugs.
5 There is only a certain amount that
the FDA can
6 do. We do not make legislation. We can
simply implement
7 what has been done, and this is an attempt
basically to
8 introduce new agents into the existing
structure. To
9 reiterate once more, we believe that the
relationship
10 between the investigators, between the
cooperative groups

and the NCI is an important one. We are here as a facilitator, working with the regulations that we have at hand -- again, we do not make laws; we interpret them and execute them. But, this is an attempt to funnel new agents, to funnel drugs that have not been properly studied to the people who we think can study them, can give us the answers that will lead to important information.

Although I am presenting it, this work has been done by many people. Dianne has been actively involved with it. Steve Hirschfield has been actively involved with it, as well as the entire pediatric team that Dianne oversees.

So, I am open for questions but really I would like to deflect the entire questions not only to myself but Dianne and Steve also since they have been active participants in

this program. Thank you.

DR. CHESNEY: Thank you very much, Dr. Pazdur. That was extremely clear and helpful, I believe, to all of us. I am wondering, Dr. Weiner, would you like to respond first to Dr. Murphy's request or wait? Okay. Yes, questions for Dr. Pazdur? Dr. Finklestein has the first one.

DR. FINKLESTEIN: I would like to make a comment, a comment that I also made at the February meeting and have made subsequently. I am probably the senior pediatric oncologist in this room, and for most of my career the FDA was "we" and "they." But, in February I concluded that it is "we" and "we," and since then I have absolutely watched what has happened at the FDA and I am convinced that it is "we" and "we." The tone that I hope we will adopt for the

rest of the meeting today will accept the fact that we really are all on the same side of the fence.

Now, since the February meeting, in the spring, with Greg Reaman, who is sitting right opposite me, who has the same hairdo so you can recognize him --

[Laughter]

-- co-chaired a meeting, and in that meeting was a group that came from the FDA, the NCI, PhARMA, the cooperative groups and the public, and the pediatric oncologists. All the participating parties were in the same room, with one goal in mind, that is, to advance the therapy

for children with cancer. So, I am convinced that the FDA will not direct, but I am convinced that the FDA will work with us in advancing the care of children with cancer.

Research is the standard of care.

Now, my colleagues in pediatric oncology I know will absolutely agree with the next statement, we spend a lot of time in the multi-disciplinary approach to children with cancer. This was alluded to by Malcolm. So, consent forms are important to us. All of us as psychologists, social workers, psychiatrists, people who spend time with our children, with the siblings, with the families, we recognize that when a child is diagnosed with cancer we change the family's life forever.

So, I look at what we are doing today as just another tool in working with this community which I mentioned, which Greg co-chaired, to advance therapy with cancer. I don't think one aspect is going to direct the other. I think we will all work together. So, I don't

consider FDAMA a threat. I look forward to finding out, as Rich Pazdur pointed out, how we can use the rule, the exclusivity, the interpretation to help children with cancer, and if you can't do it completely in the FDA, and I don't think you can, we will do it through the NCI; we will do it through the cooperative groups; we will do it through the public. I think working together we will get the job

done. Thank you.

DR. CHESNEY: Thank you very much. Dr. Friedman?

DR. FRIEDMAN: Richard, one question, for a drug that clearly is now in the Phase II or better stage for adults where a drug company has a clear indication that there is going to be a marketable agent that will produce financial gain, the plan you have outlined

seems quite
reasonable. For a drug that is in very early stages of
adult evaluation, Phase I potentially, where they are not
sure there will be any financial gain to the organization at
all, the real time where pediatric oncologists say, "gee,
we'd love to get this drug; it's in the lab, we'd like to
get access to it in the lab; we'd like to get access to it
in the clinic," there, where a company has less strong
conviction that the drug will ever produce financial gain
for them, I don't see that there is the same incentive for
them to expand to pediatrics with that and get an increase
in exclusivity which may never be of any meaning to them.
How do we deal with that issue?
DR. PAZDUR: I think that potentially is a problem
because, obviously, exclusivity has to be

attached to a
22 patent, in a sense, or something that is in
existence. We
23 have been making efforts to basically promote
this when we
24 meet with companies in all of our meetings,
whether it be
25 end of Phase I meetings or IND meetings, to
encourage them

1 to participate in this.
2 I would hope also that there may be
some
3 competition even within the cooperative groups -
- not
4 competition within the cooperative groups but if
multiple
5 agents are coming forth obviously there is a
limited number
6 of patients to be entered on these protocols,
and perhaps
7 this would provide an incentive for the
companies to come to
8 the pediatric groups earlier on in the course of
the drug
9 development process.
10 DR. FRIEDMAN: Let me follow it up

with one more
11 question that may reflect my ignorance of the regulations,
12 but if you have a company with a reasonable portfolio of
13 agents that are out there that are being evaluated, some of
14 which are clearly being sold and yet there are clearly, in
15 the developmental side of that organization, drugs that we
16 are interested in accessing to pediatric oncology, why
17 cannot we use a carrot that says we will give you
18 exclusivity for one of your agents because we clearly see
19 the profit that will come to you from that but, in return,
20 we want to access for the pediatric oncology community
21 compounds A, B and C which may or may not ever make the
22 financial gain for your organization? Why does it have to
23 be linked to the single drug we want in pediatrics? Why not

give them a financial carrot, and the bigger the drug the more one can ask from that organization?

DR. PAZDUR: Well, we don't make laws. That is one of the problems.

DR. MURPHY: Actually, just to address that question first, that was discussed. There have been various mechanisms that have been discussed, and that is called the "wild card" exclusivity which a company would be able to apply to any of their products. I can tell you that it has been discussed. I can tell you that in looking at the economic impact of what we are doing already, it is very costly, and that is without the wild card. In other words, the FDAMA activity, as it is right now and I can't say any more than that, this is costing us, and it is one of the

things that will be discussed in the FDAMA assessment by Congress -- how much is the cost to the taxpayer and to society to develop these products for children? I am a pediatrician. I think it is long overdue. The Academy thinks it is long overdue. Many people who take care of children think it is long overdue. I just want to put forth that we have been doing the math on this and this is an expensive program and people are going to have to make a cut.

So, I just want to say, first of all, that alternative approaches have been discussed. They are even more expensive. Now, that doesn't rule them out, and people may look at that again in the re-authorization of the legislation. That may be looked at again.

I know we have emphasized how often you can't extrapolate or where the diseases aren't the same, but where a product is in-house and the disease is the same and it is early on, you could use the rule if exclusivity were not going to be applicable for some reason.

DR. CHESNEY: I think Dr. Balis has a question.

DR. BALIS: In twenty years I have probably treated two patients with colon cancer and there are reports of it occurring in kids. So, if a company comes to the FDA with an application for colon cancer you could theoretically say that it should be studied in children since it occurs, but that literally probably would take centuries to do. What is the cut-off that you have in terms of incidence of diseases to apply the rule?

DR. MURPHY: We have two criteria for

the rule.

17 One is a meaningful therapeutic benefit and the other is

18 substantial use. You can qualify under either. You do not

19 need both. So, the substantial use is 50,000 population,

20 however, there are populations which do not meet that

21 substantial use but may meet the meaningful therapeutic

22 benefit. In other words, it would provide a meaningful

23 therapeutic benefit to have the information that we need to

24 dose it and to know what the safety is for that population,

25 and then the rule would allow us to require those studies.

1 DR. HIRSCHFIELD: We haven't come to that

2 situation, and if we ever get a block-buster drug in colon

3 cancer, of which there really none right now, then we

4 potentially could face that. We have looked at

ball park
ideas of several hundred cases which would sort of be a
threshold.
I would just like to reiterate something that
Jerry Finklestein said to answer Henry Friedman's question,
and that is the working together approach because we are
very excited about having colleagues who are pediatric
oncologists and industry, and many of them took time out of
their schedules to be here today with us in the audience,
and we think by having advocates in the companies, as well
as inquiries from the NCI, as well as inquiries from the
cooperative groups and the investigators, as well as
inquiries from the parents and the patient advocacy groups,
as well as receiving letters of invitation from us to
participate that we hope that that combination

would be
19 sufficiently persuasive that these new drugs could be made
20 available.
21 DR. PAZDUR: The other point I want to mention is
22 I think we have to have some integrity and credibility here
23 in the application of these rules. To try to extrapolate
24 and say that colorectal carcinoma or breast cancer or lung
25 cancer is a pediatric disease I think would produce a lot of

1 problems with our sponsors. Okay? And, although we might
2 like to exert a heavy hand, there are situations that I
3 think for the sake of continued really good faith effort in
4 promoting this, we should look at this in a very objective
5 fashion.
6 DR. CHESNEY: Dr. Reynolds, did you have a
7 question?

DR. REYNOLDS: Yes, thank you. Within the Children's Cancer Group, strategy group for neuroblastoma as well as the new approaches to neuroblastoma therapy consortium, as well as we think probably within the Children's Oncology Group as this is formed, we have a stated commitment to do development of agents based upon good preclinical data, and we have relied for the most part upon large numbers of cell lines available in vitro to determine activity for most agents, and that has served us well. One of the frustrating components of this has been in getting access to new agents as they are being developed within the pharmaceutical companies, and I know there is discussion of using this sort of preclinical modeling to develop priority schemes within the

Group beyond just neuroblastoma that would address some of the questions such as Susan has addressed, and that is, what is driving what we are going to do within the testing here. Is it the need to test an agent for exclusivity or is it the

science? And, since there are limited numbers of patients, good preclinical models are extremely important in developing the prioritization of doing Phase I studies.

You mentioned facilitation with the FDA. Can the FDA facilitate getting these agents early on into the laboratories of investigators studying pediatric cancer so we might see if they have some promise and warrant further testing in children rather than just adults?

DR. HIRSCHFIELD: A good point, an interesting strategy. Our grip is essentially when something is made

available for clinical use, and for the most part that is where our responsibilities and our mission lie. In terms of making agents available for laboratory studies, we don't have any regulatory authority.

DR. REYNOLDS: Have you had problems obtaining these agents? Because my experience in the academic world has usually been that companies have given the agents out for preclinical studies. We, for example, have wanted to study any farnesyl transferase inhibitor in neuroblastoma and I don't know of anyone who has been able to do such in vitro, certainly not in my laboratory.

DR. PAZDUR: Here, again, I would like to reiterate that the decision of what drug should be studied by a specific cooperative group is not an FDA decision. Obviously, it is that group's decision and it

should be made on your scientific assessment, whether it be on preclinical assessments or on perceived clinical potential of the drug.

DR. REYNOLDS: True, but we are not getting access to these, nor is industry even returning phone calls or letters requesting access to these agents. So, if there could be some facilitation through the cooperative group and the NCI by FDA for getting agents in for preclinical testing I think we would all benefit, including the companies.

DR. PAZDUR: We heard that, and we will make it a point in our discussion with the companies when we meet with them on preclinical matters.

DR. CHESNEY: Dr. Spielberg?

DR. SPIELBERG: I think we are all struggling with a lot of issues here. On the other hand, I

think a
15 perspective that Dr. Finklestein put forth is absolutely
16 unique. Probably in no other area of pediatric therapeutics
17 right now do we have the opportunity to make such changes as
18 we do here. The presentations this morning had better
19 science than almost any other therapeutic area that this
20 group has dealt with but even more important is what Dr.
21 Finklestein emphasized. We have here representatives from
22 the best pediatric clinical organization for doing
23 investigation anywhere in any therapeutic area. There
24 really is a network. Other groups talk about networks;
25 there really is a network.

1 Even more important, we have the cognate of COG if
2 you will within industry of pediatric oncologists now within

the industry who have been trained mostly from the same kinds of programs. The issues of early access apply really throughout all therapeutic areas, but often there are no advocates within industry within whom the pediatricians who are taking care of the patients can actually interact. Our best hope, I believe, for those early interactions and for solving the issues of exclusivity and coming up with other novel ideas is the fact that we have real advocates within the industry, coming from the same programs, dealing with the same patients, trained under the same circumstances, who recognize these issues.

Having spent 25 years on the other side in pediatric clinical pharmacology, I had the same frustrations in all sorts of different therapeutic areas of calling a

company blindly and ending up with no one to talk to, and being turned down repeatedly. The whole issue of early access, of working out these programs, of trying to get advocacy within companies is having, if you will, plants within companies, and we have the unique opportunity here because we have a large number of pediatric oncologists within companies who can act as advocates, and many of whom are here today and are active participants in that process. In no other therapeutic area do we really have that same

kind of opportunity.

So, the issues of early access is in knowing whom to call. You know, it is the old ghost-buster story. The issue here is that we have ghost busters now lined up in multiple different companies. Is it always

going to work?

Of course not. If it works with a couple of compounds that

the COG needs to get into early evaluation and preclinical

models, that is where it is going to happen. It is going to

come from personal contacts and interpersonal contacts.

If we need advocacy to solve the kinds of things

that Dr. Murphy was talking about, either modifications of

FDAMA or wild card approach because of the nature of things

-- for example, we are already doing very well with all of

the ancillary drugs that are used in oncology that keep

children alive, the antibiotics, the things that relieve

pain, the things that relieve nausea -- those all work

pretty well under FDAMA right now. There may be a way of

saying, okay, if you are working on compounds that are used

in oncology, somehow or another working out some mechanism

as those compounds get more benefit because you are also

working on a compound which is a very orphan drug that you

are introducing to actually attack the tumor -- there may be

creative ways of doing this, but the way that we are going

to do it is exactly what Dr. Finklestein described at the

beginning, the fact that there is incredible good will

within the agency right now, as well as pediatric

oncologists within the agency, pediatric oncologists in

industry and pediatric oncologists out there actually doing

the studies and treating the kids.

So, I think while, indeed, the cup is still half

empty and we have a long way to go, I feel it is more than

half full because we have all these people here today, and

all these people are listening and they are listening to Dr. Weiner's concerns; they are listening to the concerns of the oncologists. It is not going to be simple, but the bottom line is if it is important and it needs to be done, it will be done in the context of all these people working together.

DR. CHESNEY: Thank you, Dr. Spielberg. Dr. Nelson?

DR. NELSON: In listening to this, I guess in the form of a comment I am going to ask a question about FDAMA and see if there is an angle on this early access that might be viable. My understanding of FDAMA is a company needs to respond to a written request. The written request is shaped by the notion of what might be in the interests of pediatric patients and in the public health. It strikes me that

cooperation at the level of the formation of the written request from the standpoint of preclinical modeling of what drugs ought to be in the pipeline, and the like, that at the written request level one could focus those to compounds that the oncology community truly wants to use. So, it would then be driven by science and by the priorities of COG within the formation of the written request.

A couple of concerns though, since the motivation to use the rule instead of FDAMA is at potentially sunsets, unless it gets approved which is where I think some of the warnings about expense come in and the political process, if a written request is issued before it sun sets but, yet, there hasn't been a response I don't know what the situation would be in terms of allowing that exclusivity to still

exist. I am also not clear about the impact of the exclusion of biologicals and how that is defined in terms of some of the new agents that are trying to do antibody-mediated sort of attacks at receptors and that sort of thing, and whether that is a loophole in the application of FDAMA.

DR. MURPHY: Let me try to address first the preclinical part. FDAMA is very clear on that issue. We have to ask for clinical studies and they actually routinely are pharmacokinetic studies. Even though they are done in human beings, they are not considered in that category but for FDAMA they are because of the recognition that for pediatric development dose-finding, extrapolation, all those issues are relevant. So, FDAMA requires us to ask for

clinical studies.

However, when we issue a written request, and we have done this, where we think there is critical information, preclinical information that needs to be developed, we have included it in the written request as an informative process that we will be looking for this, but it cannot be an element of meeting the terms of the written request. Does that make any sense?

DR. NELSON: It makes sense, but I guess somehow you need to decide who to write that letter to and about what if part of the process of cooperation is at that level, not at the level of asking the company to do the clinical studies but at the level of deciding which compound to focus a written request to -- if that is where the cooperation takes place.

DR. MURPHY: Right, that is what we are trying to construct with this approach, that we work with the cooperative groups in issuing written requests that are targeting those priority products because of all the issues that you have heard brought forth today. That is a real concern to us. You know, we really want to maintain -- we think our goal is a public health goal here and to maintain that public health goal we need to have a cooperative approach to developing the products for which we would issue written requests, and that is what this structure is supposed to assist in doing.

DR. NELSON: Right. I guess just one brief question, in facilitating getting certain compounds into the preclinical testing -- I mean, I would think if

you were a
company with a certain compound, if you heard rumors that
there was an interest in developing a written request on
that compound and that a certain physician wants to do
preclinical modeling, I think it would be in your best
interest to send that compound to that person. So, doesn't
that begin to make some of these connections in the pre-
written request phase that are being asked for?
DR. MURPHY: Yes, it appears to make good sense.
One would hope it would work that way. What we are trying
to say is that we have certain constraints within which we
have to work. We wish to develop the science and have them
putting in these -- I won't use the word requests but the
recognition of certain preclinical areas that we think are
important and, again, doing that in this

context, the
oncology context with the process that you have heard
outlined today.
The question you had about sunset, I try never to
answer this question because I am always saying something
incorrect legally, but my understanding is that if we have
issued a written request for a product that is on the market
prior to the sunset, they can bring in the studies after the
sunset and it would still be able to gain that exclusivity.

Now, I have been very open about this, that I am
hoping Congress will not have this exclusivity sunset
because I think it is the engine that is driving product
development for children and also the science in many areas.
DR. CHESNEY: Dr. Boyett, do you have a question?

DR. BOYETT: Yes, I have a question for Richard.

Throughout your presentation you alluded to the need to have well designed studies, and I think most of us agree that our clinical trials should be based on sound statistical science with a design that specifically addresses the study objective. If your study comes from the cooperative groups, I don't have real concern because I know the design at a very high standard will address the study objective. I don't know how the FDA can provide assurance that these studies will be well designed if they don't come through such a mechanism because, as I understand it, the FDA is not authorized to critique a study design.

DR. HIRSCHFIELD: Yes, I will address that. We critique study designs all the time --

[Laughter]

-- the question maybe is do people listen to us?

[Laughter]

But when a study comes in, there are some circumstances where we review the study design in detail. For a new IND, study designs are reviewed in detail. When

someone submits a study design which they say is for a pivotal study for registration, we review that in detail. There are a number of other protocols that fall in between where we do not typically send out our comments. We look at them but, unless we are requested, we don't send out comments.

In terms of the pediatric written requests and pediatric studies in general, we look at the studies in great detail, and when we say great detail it means at least -- at least two physicians reviewing the

protocol plus at
11 least two statisticians reviewing the protocol and, if need
12 be, we also have biopharmaceutical consultation and toxicity
13 consultation.
14 DR. BOYETT: If I could just follow up, I would
15 hope that you would provide comments, especially for these
16 that are going to argue for exclusivity for their drug. We
17 have had the experience in Memphis, just this past year, of
18 an investigator coming to us with a "FDA approved" trial for
19 our scientific review committee to approve, and the study
20 design was absolutely inadequate for addressing the study
21 question.
22 DR. PAZDUR: It is difficult to comment on a
23 specific example. You know, we do not approve protocols; we
24 let them proceed, in a sense. So, you know, this concept of

25 does the FDA approve a protocol -- no, technically they are

1 allowed to proceed and depending on what level of risk we

2 are looking at, different protocols obviously undergo

3 different levels of review. Some are even exempt from FDA

4 review if they are using commercially available drugs in

5 safe doses, and recognized routes, without a commercial

6 intent, or commercial intent on claim. So, in a sense, it

7 really depends on what the protocol is.

8 I think in this situation where we are talking

9 about pediatric oncology and the fact that these are being

10 done with a commercial intent by the sponsor in terms of

11 exclusivity, obtaining exclusivity, these would be looked at

12 quite closely.

13 DR. MURPHY: Could I just say one more thing? I

think that we are often accused of many dastardly deeds, but one of the things in the process, as has been pointed out, is that we allow a protocol to proceed, and we have a mechanism called a "hold" mechanism. We have very strict guidance and regulations as to how we can put a protocol on hold, and we have an entire activity surrounding a reporting mechanism and when we put a protocol on hold. I guess I can say we could argue probably for a long time about how a poorly designed protocol is a safety issue but, in general, we cannot put a protocol on hold unless it is a safety issue or clearly has to be put on hold for concerns that we can articulate and can justify. Having a design that we don't

agree with -- usually it is not within our power to put the

protocol on hold unless it crosses a certain threshold.

Basically, as I say, it is just totally clear that it will

never be able to achieve the ends that it is intended to.

One could argue that that is a safety issue but, in general,

what I am trying to say is that the areas in which we can

tell an investigator that they absolutely cannot proceed are

limited compared to the number of protocols which are not

designed the way we would like them to be designed, but may

still achieve the ends that researcher feels that they could

achieve. So, there is a huge spectrum in there, as you can

imagine.

DR. PAZDUR: Here, again, I think there is this

basic misconception, that is, we do not approve these

protocols. This is not like NCIC that has a vested interest

in these protocols. These are allowed basically to proceed rather than a formal approval process.

DR. SPIELBERG: I would like to make one quick comment though because I think it is important that people understand the FDAMA process as opposed to most typical protocols. The written requests really provide industry a great deal of specificity, down to the number of patients, the endpoints to be evaluated, the duration of the trials, in much greater specificity than is typical for the average drug study where the sponsor says, "oh, I'd like to study X

indication," and then design a protocol which is then submitted to the agency for review. In setting up the written request a great deal of specificity, including the indication, the precise number of patients,

the precise
nature of the study -- because at the end of the day,
provision of exclusivity is dependent on the agency
reviewing step by step the written request against the
material.

So, in fact, the agency really has a great deal
more control over the nature of the studies done under FDAMA
than under typical studies, and one would certainly hope
that in areas where there is difficulty designing studies
the input comes from the subspecialists, etc. to make sure
that that negotiation which goes on with the FDA results in
a protocol that truly is going to get the information the
kids need and I think that process has worked extremely
well.

DR. PAZDUR: One of the other features, we meet

with sponsors on a continuous basis, going over these protocols and for important protocols such as this that we are looking for implementation in this program, we would probably meet with the sponsors and go over them.

DR. MURPHY: I guess one of the confusions here is that maybe we are talking about two different activities when we talk about the hold issue and we talk about the

general procedure. What Steve is addressing is the written request process which is very different. The process for drug development for children under FDAMA is very different than the routine process because FDA does have tremendous amount of authority in what they ask for in their written requests, and that is why it is very important that we have

expert input and cooperative effort.

I would also like to say that for any serious or life-threatening disease we will meet with the sponsors early on in the development of the product. Again, this is not FDAMA; this is just in general but particularly when you look at the Pediatric Rule. There are many aspects of this and it clearly tells us for all pediatric drug development that we will meet with the sponsors and talk about their pediatric plan for serious and life-threatening diseases at the end of Phase I, and for other non-serious or life-threatening diseases at the end of Phase II. That is in our regulations.

So, we are meeting with our sponsors. But, again, it comes back to what I said the first time, it is advising but what we would want them to do, what we will

do, and
22 where we will come out in the end are sometimes not always
23 the same. However, under the rule, again, we can require
24 studies and we would work with the sponsor in developing
25 what those studies are, but that is a different process than

1 the exclusivity process.
2 DR. HIRSCHFIELD: And, our written request
3 template says that the trial designs should have the input
4 of pediatric oncologists, and all the studies should be at
5 facilities which are specialized in the treatment of
6 children with cancer. So, that is a condition generically
7 of the written request.
8 DR. CHESNEY: We don't have anybody scheduled for
9 the open public hearing, and we have three people who have
10 been patiently waiting to ask their questions here, and we

want to give Dr. Weiner a chance also. So, my thinking is that we allow these three people to ask their questions, and any comments from Dr. Weiner, and plan our break at 10:45.

Dr. Friedman?

DR. FRIEDMAN: I think it was covered.

DR. CHESNEY: Dr. Gorman?

DR. GORMAN: I would like to make a comment and then ask a question of Dr. Spielberg. As an outsider, it seems to me that both the Oncology Group and the Food and Drug Administration have worked very hard to try to fine-tune FDAMA and the Pediatric Rule to move children's studies further on. But one of the things I have learned sitting on this committee is that the FDA is restricted because it doesn't make laws; it only interprets laws that are presently on the books.

There is also the question about early clinical access for people to drugs that are in development by pharmaceutical companies, and I would like to posit to you, before I ask the question of Dr. Spielberg, that you are still intervening in the process way too late, and this is not under the aegis of the Food and Drug Administration but may be something that the group that sits across the table from me would strive for.

It strikes me the chemical moieties need to be studied for pediatric cancers rather than being studied strictly for adult cancers and then being adopted for pediatric cancers, and my question to Dr. Spielberg is in the development of new oncologic agents, are there panels in the early testing of clinical moieties before clinical

trials are even considered, specifically designed for the biology that we know about pediatric cancers? Because this is one of the few areas where we have enough biological information to do early tests on those types of agents?

DR. SPIELBERG: I am really not the person to ask in terms of the biology. I think the generic question though is in the screening processes that normally go on within companies or, for that matter, at NCI, do we have enough validated models preclinically that will suggest a pediatric applicability of a given compound early enough so that that compound -- for example, there may be a situation

where it doesn't work in any of the adult preclinical models but might give hits in the pediatric model. You know, take

the tumor type that is atypical for pediatrics and is there a unique pediatric disease? The real question is how predictive are the models, and are they currently being included in the general screens, and I have to defer that to the oncologists.

DR. GORMAN: I would like to just follow that up because I realize that is a very specific question to ask somebody with very general knowledge, but there are three programs, as far as I understand it, that now allow -- or that our government has tried to make available to children drugs. One is the Pediatric Rule, the second is FDAMA and the third is the orphan drug program. All three were, hopefully, designed to test or promote the development of pharmaceutical agents in small populations, and one of those

should be tinkered with, in whatever legal way things get tinkered with, to allow for us to reach back because in this particular area there is enough biological -- I realize there is a long way from testing chemical moieties until they become clinical agents, but there needs to be a reaching back far enough downstream that you are not left in the position of using drugs that show promise for big diseases and then have the development of agents specifically for the biological of your diseases.

DR. SPIELBERG: I would point out comfortably as well that FDAMA can be applied to orphan drugs so that if you do have an orphan -- if you have any kind of exclusivity, including orphan drug exclusivity, you can get an additional six months.

DR. CHESNEY: Dr. Smith, were you

going to
respond?
DR. SMITH: I was just going to echo Dr.
Spielberg's comment that there is a real question about what
the validity of the preclinical screens are, both in the
adult models where they are applied by drug companies but
how effective they are, and in pediatric cancers as well.
We, at the NCI, do recognize this is a priority
area and researchers in the Children's Oncology Group
recognize this is a priority area, and we are working
together to try to development a pilot program that would
facilitate the screening of new agents, and to do it in a
rapid way so that the information is actually useful in
considering the prioritization of agents. But, we have to
do this recognizing that the systems for the

preclinical
21 screens as of this time aren't validated as to whether they
22 really are predictive, and what shows as promising in a
23 preclinical screen isn't truly validated as being an agent
24 that is going to work for a particular type of cancer.
25 DR. GORMAN: Being relatively a newcomer to this,

1 with only 12 years of interest in this particular area, it
2 strikes me that these same screens do predict for the
3 pharmaceutical companies a pathway on which to go down,
4 which agents show initial promise, and then more from there
5 forward. And, in the restructuring of these laws, perhaps a
6 financial incentive for the companies that is meaningful
7 would allow that process to develop much more rapidly.
8 DR. SMITH: And, we think as well that

the use of
NCI funds for researchers to study new molecular targets and
new agents is an appropriate avenue to pursue as well.
DR. CHESNEY: Dr. Fink?
DR. FINK: My comments were essentially the same
as Dr. Gorman's, and I think if NCI is already doing it,
obviously getting these preclinical screens into the hands
of the pharmaceutical industry is one of the answers to the
availability question, and it clearly falls outside, I
think, the Pediatric Rule of FDAMA because these are really
orphan diseases and the Pediatric Rule isn't going to apply
to most of them in terms of numbers.
DR. CHESNEY: One more question, and then Dr.
Weiner and then our break.
DR. COHN: Yes, I was just wondering in terms of
the Pediatric Rule, if someone could just

clarify, if you
24 have a class of drugs that is not necessarily
tumor specific
25 but pathway specific, for example, the anti-
antigenic agents

1 which potentially could be used for adult cancer
and
2 pediatric cancer alike, does the Pediatric Rule
apply to
3 that classification of drugs?
4 DR. HIRSCHFIELD: Dr. Cohn, stay tuned
for this
5 afternoon. That is going to be their topic of
discussion.
6 DR. CHESNEY: Thank you, Dr.
Hirschfield. Dr.
7 Weiner, any concluding comments? Questions?

8 DR. WEINER: Yes, just two comments to
response to
9 what Dr. Murphy had asked and also just by way
of summary
10 from our perspective, and this is a remark that
I made
11 actually in the meeting in February that Dr.
Finklestein
12 referred to which is that from our

perspective time is
really the issue. In implementing FDAMA and the Rule, time
is really the question. How long does it actually take to
Phase I and Phase II trials in kids, and what is the meaning
of that in terms of "incentivizing" the pharmaceutical
companies to do this in pediatrics? Will it be worth it?
From our perspective, anything that really impedes the
progress and the efficiency of the systems involved in
evaluating agents and getting new information that is going
to be useful for treatment or kids is a bad idea. That is
all we have got.

The second point I really wanted to address had to
do with flexibility. I think, you know, the conversation
today has yielded a lot of interesting suggestions about how

greater flexibility might be brought to bear with respect to FDAMA and with respect to the implementation of the Pediatric Rule, both formal in terms of the redesign of FDAMA specific provisions for cancer perhaps and, in addition, an informal mechanism such as that which was suggested by Dr. Spielberg and by others, picking up on the notion that, yes, there are informal contacts in industry and personal contacts that, hopefully, will be of benefit but there are also opportunities to bring FDA to the table, as happened in February, so that we can come up with more creative solutions to getting new agents, evaluating new agents, as well as understanding agents that are already approved and already in use in treatment for kids so that we can have sufficient information about those as

well.

DR. CHESNEY: Thank you for your very thoughtful comments, and I understand there is Valium outside for our FDA colleagues who I think have stood up extremely well to the challenges presented this morning.

I would like to reiterate what Dr. Finklestein said, that I really believe this is a "we/we" situation and not a "we/they" and, please, be back by 10:55 and we will attempt to address the question that the FDA specifically gave us. Thank you.

[Brief recess]

DR. CHESNEY: We are past the time for the open public hearing and nobody has signed up but if there is anybody here today that would like to make a comment at the microphone, this would be a good time to do so.

Yes?

DR. REAMAN: I would just like to make a comment because, as Dr. Finklestein referred to earlier, I was at this meeting in February where there was a great deal of discussion, and certainly the end result of that meeting was that this is a "we/we" situation and we are working together very collaboratively.

Subsequent to that, in review of the guidance that was put forth from the FDA there were some concerns as related to flexibility to some of the interpretation, but I must say from my perspective now, being responsible for developmental therapeutics and sharing that responsibility in the Children's Oncology Group, I see absolutely nothing about the guidance which would limit the early access to new agents for children with cancer, and I would

really applaud
19 the FDA in everything that they have done to interpret and
20 to remove any obstacles from the Pediatric Rule and FDAMA in
21 ensuring this. Thank you.
22 DR. CHESNEY: Thank you, Dr. Reaman. Any other
23 comments? If not, we need then to go on to the question to
24 the committee, and I wondered if Dr. Hirschfield, Dr. Pazdur
25 or Dr. Murphy would like to read it or interpret it for us,

1 or do we take it as written?
2 DR. HIRSCHFIELD: I think you could take it as
3 written. I could just read it out loud for those who may
4 not have a copy of the question: Special characteristics of
5 pediatric oncology necessitated a more general drug
6 development plan to qualify for the FDAMA pediatric
7 exclusivity incentive. These characteristics are rarity of

the diseases, life-threatening natural history of the diseases, biological differences between adult and pediatric tumors, the existence of established cooperative groups, and research protocols as the standard of care. Are there other areas of pediatrics that have similar characteristics that may benefit from a similar approach?

Discussion

DR. CHESNEY: Thank you. Comments from the committee? Yes?

DR. PRZEPIORKA: The information that we have been given so far yesterday and today indicates that extension of exclusivity is for drugs and biologics, and I was wondering if this is also true for devices, such as catheters or transdermal delivery systems, or diagnostics for pediatric diseases.

DR. MURPHY: The rule includes

biologics. Now, if
24 you look at the list that we did publish under
the FDAMA
25 requirement, it did include some biologics
because we did

1 not look at whether something had a patent or
exclusivity,
2 and because biologics normally don't have
patents -- that is
3 why exclusivity is not usually including those.
So, I am
4 just trying to recognize that there is a little
bit of
5 confusion about the fact that we did have some
biologics on
6 that list. We were trying to look at products
that we
7 thought would have a public health benefit
potentially if
8 they were labeled so they were on the list.
But, again, as
9 Dr. Pazdur said, you have to have something to
attach it to
10 for exclusivity to work. So, that is a problem
in that most
11 biologics are not approved where they have that
patent

mechanism. So. Devices -- no. It does not apply to that either.

DR. CHESNEY: Other conditions which might qualify as pediatric oncology has? Dr. Fink?

DR. FINK: Well, the two groups that I deal with, cystic fibrosis, although there is a strong national organization there, and the other would be the neuromuscular disorders and, again, there is a strong voluntary health agency that has somewhat taken leadership in those two diseases, but they are similar in that they are life-threatening; they are orphan diseases; and there are care networks through the CF centers and the NMDA centers.

DR. CHESNEY: Dr. Luban?

DR. LUBAN: I would like to add to that group

sickle cell disease. Now, while it might not be

life-
 2   threatening it certainly is quite morbid
and there is,
 3   through the sickle cell centers sponsored
by NHLBI, a
 4   growing clinical trials network.
 5   DR. CHESNEY: Maybe I could add one
group. I
 6   don't think we have any pediatric nephrologists
in the room,
 7   but having lived with one for 30-plus years --
 8   [Laughter]
 9   -- who has devoted his career to
trying to bring
10   rare pediatric diseases to the attention of
Congress, and
11   their needs, I would just like to say that
there are many
12   renal diseases that also fall into the same
category as Dr.
13   Fink just mentioned. They are relatively rare.
They have
14   very strong support groups, and I can't
elaborate on them
15   but maybe somebody else in the room can but
there is a very
16   elaborate nephrotic syndrome network of

investigators that would be similar to some of the pediatric oncology groups.

Yes, Dr. Luban?

DR. LUBAN: Perhaps Dr. Hudak or Ward could comment on the use of the neonatal networks for some clinical trials, particularly in prematures.

DR. HUDAK: Sure, the neonatal network is an NIH sponsored group of study centers for which there is competitive application by sites. It is headed up under NIH CD. I think it has been in existence now for 15 years, and

the network I think is a good example of how cooperation between NIH and academic centers can produce some meaningful and important results, and it also illustrates, frankly, some of the perils of doing large, multi-center trials where there is a significant lag phase in terms of an

idea gets
6 developed and when it gets implemented, and what happens in
7 the interim in the clinical centers. But, this has led to
8 some important information and clarification of therapies in
9 neonatology, and that is a little bit different model than
10 the orphan type diseases because we are never at a dearth of
11 neonates, and it does target some of the important
12 morbidities that we see in premature babies.
13 DR. WARD: I think the other area that is actively
14 involved in multicenter trials is that of the pediatric
15 pharmacology research units. Dr. Kauffman wanted to comment
16 about it, but that has allowed also multicenter trials to
17 proceed in areas of very important aspects of pediatric
18 therapeutics, and to proceed fairly efficiently.
19 DR. CHESNEY: Yes, Dr. Balis?

DR. BALIS: The other disease I want to raise is neurofibromatosis, which is a disease that shares a lot in common with cancer and which many of the new agents that we are developing that are molecularly targeted may have application, but at this point there really is no other standard therapy, other than surgery.

DR. CHESNEY: Several other categories that have occurred to me are the immune deficiency diseases; chronic granulomatous disease, very small numbers of patients, inevitably fatal, and I don't know about their support group but certainly SCIDs and some of the other better defined genetic immunodeficiency diseases have very elaborate support groups and networks. Then, the whole area of

genetic and metabolic diseases, again, cystinosis falls in that category but probably other people here can think of many more of those. Dr. Danford?

DR. DANFORD: I wish I could say that pediatric cardiology and heart disease had things in common with the research protocols and networks available in oncology but, unfortunately, I can't. There are scattered examples of multicenter trials but, by no stretch of the imagination, can we say the standard of care equals Phase III trials even in cardiology conditions that are treated with medicines rather than surgeries.

The one place where we could say that there might be that kind of a situation would be in devices, and there the interventional cardiologists do have a well-developed nationwide network. Unfortunately, we just

heard that FDAMA
23 and the Pediatric Rule don't apply in those situations.
24 DR. CHESNEY: Dr. Luban?
25 DR. LUBAN: I would like to propose not a group

1 but, rather, a disease phenomenon that crosses groups, that
2 is very, very common and requires a potential application of
3 the rule, and that is in thrombosis, childhood thrombosis --
4 very, very common; unfortunately, poorly treated. At this
5 point, no organized clinical trials, although there have
6 been some moves through the hemophilia treatment centers to
7 incorporate thrombosis trials in those groups. And, with
8 the advent of all of the new low molecular weight heparins,
9 it is potentially an important avenue to explore.
10 DR. CHESNEY: Dr. Fink, I wonder if you could
11 elaborate or tell us a little bit more about

the cystic
fibrosis situation, which I thought was very analogous to
the oncology example.
DR. FINK: Well, there are 125 centers that are
partially funded by the National CF Foundation that
participate in collaborative Phase I, Phase II and Phase III
trials, and recently the National Foundation has even gone a
step further and developed eight therapeutic development
network centers that take care of the Phase I and Phase II
trials and to use the entire network for the Phase III
trials, so that there is even a gradation, and centering
Phase I and Phase II trials in larger academic centers that
have a large population and heavy research support has led
to more efficient production of Phase I and Phase II trials,
and then the Phase III trials obviously, because

of patient

needs, are spread to the wider network. That has been a combined effort that really has both federal and private funding.

DR. CHESNEY: Dr. Luban, could you tell us more about the sickle cell networks?

DR. LUBAN: The National Hearth, Blood and Lung Institute has for years funded sickle cell centers which are a combination of both basic science as well as clinical research. For many years the clinical research was very single-institution directed, and it has just been within the last three or four years that there has been more of an attempt to bring those centers together and have them do cooperative clinical investigations and the initiation now of hydroxyurea trials.

My understanding from the Branch is that they would like to do more and more clinical trials and, of course, the infrastructure is all paid for already by NIH, with nurse practitioners, data monitors, in a similar way although clearly in a much lower scaled way than the cancer cooperative groups. Certainly, also from a biological perspective, lots of animal models, SCID mouse particularly, as well as pharmacologic manipulation so that as drugs can be developed, and are being developed, there should be a mechanism to do some translational clinical trials.

DR. CHESNEY: Yes, Dr. O'Fallon?

DR. O'FALLON: I believe there is an AIDS cooperative group for children.

DR. CHESNEY: Very active network of AIDS clinical

treatment units, of which we have one at St. Jude, very actively involved in sharing data and comparing notes. Yes, Dr. Fink?

DR. FINK: Yes, one of the things that occurred to me yesterday when we were talking about psychoactive drugs is that almost all of the diseases and groups we are talking about share the issues of how do you cope at a family level with chronic disease? How do you administer chronic medications, and what do you do with the adolescent with a chronic disease? And, yet, none of the groups probably have the psychiatric expertise or maybe the number of patients to take on that issue, and there clearly is a need across pediatrics to try and understand family and individual coping and growing up with a chronic medical disability.

DR. CHESNEY: Thank you. I think we heard about autism yesterday which also very much falls into this category of relatively rare disease with a bad need for new drugs, new approaches. Dr. Ward?

DR. WARD: I would like to just provide something of an overview. I think we have just heard of multiple areas in pediatric medicine and pediatric problems that need additional therapeutic research. I think FDAMA can work,

and is working in many of these. And, from the February meeting, the FDA proposed mechanism by which trials at Phase I and Phase II level could qualify for exclusivity -- we heard it in its application to oncology drugs, but there are probably many other areas of therapeutics, from cystic fibrosis to cystinosis to other inborn errors of

metabolism,
that may benefit from that process.
When it comes time for renewal, I have concerns
about trying to create carve-outs for specific clinical
areas, especially if we have a process that can serve all
areas of pediatrics effectively, because if one area is
carved out and identified as unique many other areas will
feel they are also unique, and the potential effect could be
an unwinding of congressional support for renewal. And, I
think we have to be very cautious in how we proceed over the
next 18 months as this comes up for a great deal of debate
and discussion.
DR. CHESNEY: Thank you. Any other comments?
Suggestions for other diseases which the FDA has asked for?
I guess, not having been at the February meeting but having

worked with our pediatric subcommittee for sometime, I would also like to emphasize what Dr. Ward just said so articulately. I think many of us in the room have disabled children or children with a limited life span, including myself, and I think we would all like a carve-out, if you

will, but I think that it is important that we try in every possible way to support FDAMA, and I am very impressed at what the Oncology Group has done at the FDA -- Dr. Pazdur's presentation today -- to work with FDAMA, and I just would like to reiterate what Dr. Ward said, that we should all try at every level to support what has been a historic contribution to pediatric care.

DR. MURPHY: I guess I want to second or third that because I think when you go to Congress you never know

what you are going to come out with at the end, folks. So, we have something that is working. We are working on ways to make it work better where we have identified problems. If you tinker with it too much, you don't know that you are going to get it at all, first of all, secondly, you don't know what you are going to end up with.

It is like a new child having certain infirmities and we want to trade it in for another child, I would say let us work with this child and support developing this child, if you will, because it truly is a program in its infancy. Think about what the potential would be for moving all these various fields forward, if we could ever get to the point where we actually had products that are already out there that aren't labeled and get them studied, plus

then move these developmental fields forward in all these areas of science -- we have an opportunity here, and I would

caution some restraint as we go forward and, instead of trying to fix every single problem use the tools we have been given and work with them and work to have FDAMA renewed very much in the format that it is -- not that FDA doesn't have its problems either with it, but we really believe that we are just now discovering how to work with this opportunity in the most positive way. Thank you.

DR. CHESNEY: Dr. Spielberg:

DR. SPIELBERG: I would fourth that. With the perspective of having been in pediatric pharmacology for 25 years, this really is historic. I think most of us who have been in the field for a long period of time

never would have
imagined that we would be in the position where we are today
where a lot of the past issues are no longer issues; where
drugs are being actively studied; where large numbers of
compounds which had been orphan for many, many years are now
being actively studied.

The renewal of the legislation really is crucial I
think not only to the issue of getting drugs studied, but
really also has tremendous impact on the overall activities
within pediatric departments around the country. It has
stimulated a great deal of translational research.

If I can be critical of departments of pediatrics
because I was in them for many years, even when I was junior
faculty I was told there were two things you could do,

molecular biological or patient care, and that was it, and molecular biological was too difficult for clinicians and, after all, the molecular biologists didn't understand anything about patients so they should stay away.

What this has done is revitalize the whole issue of translational research. The old model which I was taught in the '60s in medical school of bench to bedside really does have validity, of getting science to the patients who need it, and this initiative has really reawakened that in a remarkable way. It is truly critical for renewal not only for pharmacologic interventions but really for clinical investigation in pediatrics in general.

And, there are certain things that have been done around the sites independent of the FDAMA effort, and I

think that is another lesson that we can take. If there are specific issues, we can go outside the legislation to try to fix certain things. One example is that we have been working on legislation to increase the number of pediatric pharmacology trainees, you know, Ralph and I -- Bob is the only one who doesn't share our hairdo -- but we all are getting old and we recognize that so many years have gone by without pediatric departments focusing on the need for translational research that the next generation of translational researchers isn't there.

But that legislation, including some clever things

that Sen. Dodd's and DeWine's office came up with of debt forgiveness of those who go into pediatric investigation and stay in that field, along with additional

support for the
4 PPRU network to actually support the training slots that are
5 needed, is really one aspect of things that we can work on
6 independent of FDAMA, but even that initiative is truly
7 dependent on FDAMA renewal otherwise we are going to be
8 training people who won't have jobs in the long run. One of
9 the neatest things about trying to train young people is
10 that they will have jobs, otherwise why spend all those
11 years? And, FDAMA provides routes for pediatricians to be
12 involved in government, to be at FDA, to be at NIH. It
13 provides routes for them to go into industry because
14 industry will be working on pediatric projects, and it will
15 obviously provide routes for their careers in academia so
16 that the studies can be carried out.
17 So, you know, if you look at that

piece of
18 legislation for trainees and then you look at
FDAMA you say,
19 "aha, the two work together and they really do
complement
20 each other." Similarly, I think as time goes
by, I think
21 Dianne is right, I mean we have had -- what? --
a year and a
22 half experience with this, barely two; ten drugs
getting
23 labeled in the previous ten years for kids and
eleven drugs
24 getting labeled in the last year. I mean, that
is a ten-
25 fold increase in the rate of activity. And,
obviously, from

1 all the compounds that are now being studied,
all those
2 things will lead into labels. We have made
mistakes and we
3 have realized knowledge gaps. Those knowledge
gaps then can
4 be turned into support for NIH funds to study
those disease
5 processes so that we can get outcome variables

that we can
study so that we can, in fact, get drugs properly labeled
for kids. It all kind of beings to work together. But
critical to the whole effort really is getting FDAMA renewed
and keeping the process going.
DR. CHESNEY: If I could just make one more
comment, my husband, for those of you who don't know, is the
chairman of our department but if I had a dollar for every
time he has come back from a meeting at the NIH or Congress
and said, "I can't stand these internists; they forget that
children aren't just little adults and that we absolutely
need to focus on pediatric issues." And, I think there have
been many positive outcomes of his work and many others, the
PPRUs is just an incredible idea. Maybe, Ralph, you can
tell me sometime whose idea it was, but these

centers that
are just devoted to studying drugs in children
are just
revolutionary. And, I think in so many ways
FDAMA
represents this major new movement in support of
children
that I would just add again to Dr. Spielberg's
always
articulate comments that it is really critical
that we try
to work within the system or we will be back
where we were

when internists ran the show -- apologies to any
internists
in the room! Any other comments? Ralph?

DR. KAUFFMAN: I would just add
briefly to Steve's
comments, and that is we need to understand that
renewal of
FDAMA is not automatic. There is very powerful
opposition
out there that will be doing everything possible
to try to
see that FDAMA is not renewed, and will be
lobbying whoever
is in Congress next session very aggressively to

try to keep
this legislation from being renewed. So, it isn't going to
be automatic, and all of us are going to have to engage in a
concerted effort, those who have the welfare of children at
heart, to make sure that this gets done because it certainly
is not a sure thing.

DR. CHESNEY: Thank you. Dr. Ettinger?

MS. ETTINGER: I just feel, from the unique
perspective of being at the bedside as a nurse, I can
reiterate what Susan had said. It is really important that
we put concrete measures from bench to bedside because it is
our parents and it is the families who actually drive this
including parent support groups in all of these, they are
the ones who actually bring it forth and I think it is most
important that we continue that.

DR. CHESNEY: Dr. Murphy, the last word.

DR. MURPHY: I just want to thank you for your thoughts and the fact that, as we move forward in each of

these areas, we will be bringing different issues to this committee, again usually supplemented with the subspecialists, as you saw yesterday with neuropharm., and actually they have been one of the more active participants in this last year and a half in trying to help us to develop priority setting in how we move forward in this area. And, we will, as always, listen to what you have said as far as some of the areas that we may need to look at in our future written requests as we try to move the science and the information that is available. Because -- it a very good point to end -- what are we trying to do? People say why is

the label so important? Because that is FDA's way of providing the science and the information. Now, we are hoping to develop other mechanisms and being able to transmit the information to the public in other ways besides just the label, but for right now the label is our main say of communicating to both the professional and, through some of our package inserts and med. guides, to the patients and the families. And, that is the goal. The goal is that you will have the right information, meaning you will know how you are dosing the child. The mother and father have the expectation that when their child receives that medicine it will have been studied and we will know that it will work, and we will know how to advise them as to how the adverse effects are. So, we are expanding this

spectrum of the
preclinical all the way to not just the bedside in the
hospital but the bedside at home in the middle of the night
when you should be able to expect something as simple and
common as your anti-pruritic to have the right dose. So,
thank you all very much.

DR. CHESNEY: I want to thank all of our speakers
today. I want to thank Dr. Smith, Dr. Weiner, Dr. Pazdur,
everybody who made contributions and comments this morning.
I think this has been a very, very informative session for
those of us who are not oncologists.

This meeting will reconvene at one o'clock.
Yesterday lunch was in the Plaza Cafe and there was room
reserved for the FDA; we are not sure if that is true today.
I think our executive secretary has an

announcement.

DR. TEMPLETON-SOMERS: I just want to clarify this afternoon's meeting because I think there might be some confusion. The pediatric subcommittee of oncology will convene at one o'clock in the Chesapeake Suites to talk about the extrapolation issue, and the pediatric subcommittee of the anti-infective drugs stays in this room and you will be meeting also at one o'clock.

DR. CHESNEY: Thank you very much.

[Whereupon, at 11:34 a.m., the proceedings were recessed]